IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL, SRL, and ORTHO-MCNEIL, INC.,	)	Civil Action No. 07-255-KAJ (CONSOLIDATED)
Plaintiffs/Counterclaim-defendants,	)	
v.	)	
PAR PHARMACEUTICAL, INC., and PAR PHARMACEUTICAL COMPANIES, INC.,	)	
Defendants/Counterclaim-plaintiffs.	)	

FINDINGS OF FACT AND CONCLUSIONS OF LAW

Jack B. Blumenfeld, Esq., Morris, Nichols, Arsht & Tunnell LLP, 1201 N. Market Street, Wilmington, Delaware 19801
Mary W. Bourke, Esq., Connolly Bove Lodge & Hutz LLP, 1007 N. Orange Street, Wilmington, Delaware 19801; Counsel for Plaintiffs/Counterclaim-Defendants, Purdue Pharma Products L.P. and Napp Pharmaceutical Group Ltd.

Of Counsel: Robert J. Goldman, Esq. Ropes & Gray LLP, 525 University Avenue, #300, Palo Alto, California 94301
Sona De, Esq., Ropes & Gray LLP, 1211 Avenue of the Americas, New York, New York 10036

Frederick L. Cottrell, III, Esq., Richards, Layton & Finger P.A., One Rodney Square, Wilmington, Delaware 19801; Counsel for Defendants/Counterclaim-Plaintiffs.

Of Counsel: Daniel G. Brown , Esq., Wilson Sonsini Goodrich & Rosati, 1301 Avenue of the Americas, 40th Fl., New York, New York 10019
Ron E. Shulman, Esq., Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, California 94304
Nicole W. Stafford, Esq., Wilson Sonsini Goodrich & Rosati, 900 South Capital of Texas Highway, Las Cimas IV, 5th Fl., Austin, Texas 78746.

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JORDAN, Circuit Judge[1]

I. INTRODUCTION

This is a patent infringement case. Purdue Pharma Products L.P. ("Purdue") and Napp Pharmaceutical Group Ltd. ("Napp") (collectively "Plaintiffs") have sued Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc. (collectively "Par"), in connection with Par's Abbreviated New Drug Application ("ANDA") and its manufacture, use, and intent to sell generic versions of Ultram® ER ("Ultram ER"). Ultram ER is an extended-release tramadol hydrochloride pain relief medication. (Uncontroverted Facts, D.I. 326 at ¶ III.C.(27), (29).) Plaintiffs allege infringement of U.S. Patent No. 6,254,887 (the "'887 patent"), entitled "Controlled Release Tramadol," and seek a declaratory judgment of infringement of U.S. Patent No. 7,074,430 (the "'430 patent"), entitled "Controlled Release Tramadol Tramadol [sic] Formulation." Par denies infringement and responds in defenses and counterclaims that the asserted claims of the patents-in-suit are invalid and are unenforceable due to inequitable conduct. A five-day bench trial was held in this action from April 16 to April 22, 2009. The following, issued pursuant to Federal Rule of Civil Procedure 52(a), are my findings of fact and conclusions of law on the issues of infringement, validity, and enforceability of the patents-in-suit.[2]

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[1]Sitting by designation (Docket Item ["D.I."] 241).

[2]Throughout these Findings of Fact and Conclusions of Law, I may have adopted without attribution language suggested by one side or the other in this dispute. In all such instances, the finding or conclusion in question has become my own, based upon my review of the evidence and the law. To the extent that any of my findings of fact may be considered conclusions of law, or vice versa, they should be considered as such.

For the reasons that follow, I conclude that Par has infringed the asserted claims of the patents-in-suit but that those claims are obvious and therefore invalid. I also conclude that Par has not carried its burden of showing by clear and convincing evidence that the patents-in-suit are unenforceable due to inequitable conduct.

II. FINDINGS OF FACT

A. *The Parties*

1. Purdue is a limited partnership organized and existing under the laws of the State of Delaware, having a place of business at One Stamford Forum, 201 Tresser Boulevard, Stamford, Connecticut 06901-3431. (Uncontroverted Facts, D.I. 326 at ¶ III.A.(1).) Napp is a limited company organized and existing under the laws of England, having a place of business at Cambridge Science Park, Milton Road, Cambridge, CB4 0GW, United Kingdom. (*Id.* at ¶ III.A.(2).)

2. Purdue and Napp were assigned the patents-in-suit on May 4, 2007 by Euro-Celtique S.A.[3] (*Id.* at ¶¶ III.E.(48), F.(60).)

3. Par Pharmaceutical, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at One Ram Ridge Road, Spring Valley, New York 10977. (*Id.* at ¶ III.A.(5).) Par Pharmaceutical Companies, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 300 Tice Boulevard, Woodcliff Lake, New Jersey 07677.

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[3]Euro-Celtique S.A. is an associated company of Purdue and Napp in whose name the patents-in-suit were prosecuted. (Uncontroverted Facts, D.I. 326 at ¶ III.E.(47).)

Par Pharmaceutical, Inc. is a wholly owned subsidiary of Par Pharmaceutical Companies, Inc. (*Id.* at ¶ III.A.(6).)

B. *Procedural Background*

4. Biovail Laboratories International, SRL ("Biovail") submitted New Drug Application ("NDA") 21-692 to the Food and Drug Administration ("FDA") on December 31, 2003.[4] (Uncontroverted Facts, D.I. 326 at ¶ III.C.(29)-(30).) Biovail's NDA was for a controlled release tramadol formulation for once-daily dosing, under the proposed trade name "Ralivia ER." The FDA approved the application on September 8, 2005; the trade name for the drug was later changed to Ultram ER.[5] (*Id.* at ¶ III.C.(29), (30), (32); Trial Transcript ["Tr."] 699:10-700:10; Plaintiffs' Trial Exhibit ["PTX"]-879.)

5. Ultram ER is indicated for "the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time." (PTX-650 at 2.) The label also provides that Ultram ER should be taken "once daily." (*Id.* at 4.)

6. In compliance with 21 U.S.C. § 355(b)(1), Biovail certified to the FDA as a part of its NDA that the '887 patent claims cover Ultram ER. (Uncontroverted Facts, D.I. 326 at ¶ III.E.(49).) Accordingly, the FDA lists Ultram ER as being associated with the

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[4]Although Biovail continues to appear in the caption as a plaintiff, its claims and the counterclaims against it were dismissed by consent on November 10, 2008, and it is no longer a party. (D.I. 275.)

[5]Because Ralivia ER and Ultram ER are simply different trade names for the same product, I will refer to the extended release tramadol formulation submitted by Biovail to the FDA as Ultram ER.

'887 patent in a publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluation," which is generally called the "Orange Book." (*Id.*)

7. Ortho-McNeil, Inc. (now Ortho-McNeil-Janssen-Pharmaceuticals, Inc.) ("Ortho") sells Ultram ER in the United States pursuant to an agreement with Biovail. (Nature of the Case, D.I. 326 at ¶ I.2; Uncontroverted Facts, *id.* at ¶ III.C.(33).) The parties have assumed that Ortho is a licensee of the patents-in-suit.[6] (Nature of the Case, *id.* at ¶ I.2.)

8. Par has submitted ANDA No. 78-783 to the FDA, pursuant to 21 U.S.C. § 355(j), seeking approval to market generic extended-release tramadol hydrochloride tablets ("Tramadol ER tablets" or "Par's tablets"). Specifically, Par's ANDA seeks FDA approval for the commercial manufacture, use, or sale of Tramadol ER tablets in 100, 200, and 300 mg dosage strengths. (Uncontroverted Facts, D.I. 326 at ¶ III.B.(7).) Par's ANDA contains a "Paragraph IV Certification," *see* 21 U.S.C. §

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[6]As reflected in the caption, Ortho was a plaintiff in this case as well. In an earlier decision, I ruled that Ortho lacked standing and therefore dismissed it from the suit. *Purdue Pharma Prods., L.P. v. Par Pharm., Inc.*, No. 07-255-KAJ, 2008 WL 5100115 (D. Del., Dec. 3, 2008). At that time, I analyzed Ortho's license to the '887 patent only; if Ortho has a license to the '430 patent, it has not been brought to my attention. *Id.* at *1 n.3.

355(j)(2)(A)(vii)(IV),[7] which alleges that the claims of the '887 patent are invalid and/or will not be infringed by Par's tablets. (Uncontroverted Facts, D.I. 326 at ¶ III.E.(52)).

9. Par notified Plaintiffs of its ANDA filing, and Plaintiffs responded by filing this action, alleging infringement of the '887 patent under 35 U.S.C. § 271(e)(2). (*Id.* at ¶¶ III.B.(8), E.(50).) Plaintiffs also seek a declaratory judgment that the manufacture, use, and substantial preparations for the offering for sale of Par's tablets will constitute infringement, contributory infringement, and active inducement of infringement of the '430 patent. (D.I. 78[8] at 7.) Par's Second Amended Answer and Counterclaims allege that the claims of the patents-in-suit are invalid, unenforceable, and not infringed. (Uncontroverted Facts, D.I. 326 at ¶ III.E.(53), F.(62).)

C. *Pharmaceutical Background*

10. At claim construction, I determined that a person of ordinary skill in the art at the time of the invention was one with experience as a formulator (one who makes a drug), a pharmacokineticist (one who researches and characterizes the drug),

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[7]Under 21 U.S.C. § 355(j)(2)(A)(vii), a generic manufacturer must certify in its ANDA whether its proposed generic drug will infringe any patents listed in the Orange Book as being associated with the branded drug. For each listed patent, the ANDA applicant must make one of four possible certifications. As relevant here, a "Paragraph IV Certification" is one that states that the patent is invalid or will not be infringed by the generic drug. § 355(j)(2)(A)(vii)(IV). A Paragraph IV Certification makes the filing of an ANDA an act of patent infringement, 35 U.S.C. § 271(e)(2)(A), and the applicant must provide notice to the patent holder of its invalidity or noninfringement position along with the certification. 21 U.S.C. § 355(j)(2)(B). The patent holder has forty-five days after receiving that notice to file a patent infringement suit, and, if an infringement suit is filed, FDA approval of the ANDA is stayed until either thirty months have passed or a court rules that the patent is invalid or not infringed. § 355(j)(5)(B)(iii). *See generally Abbott Labs. v. Teva Pharms. USA, Inc.*, 432 F. Supp.2d 408, 414-415 (D. Del. 2006).

[8]D.I. 78 is Plaintiffs' amended complaint.

and a clinician (one with experience in treating pain). *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 584 F. Supp. 2d 664, 670 n.12 (D. Del. 2008) ("*Claim Construction Opinion*"). The parties do not dispute that determination, and I find that it continues to be the appropriate standard.

i. *Tramadol*

11. The patents-in-suit relate to oral controlled release tramadol formulations. ('887 patent, 1:22-25.[9]) Tramadol is categorized as a weak opioid analgesic used to relieve moderate to moderately severe pain. (Grond,[10] Tr. 981:1-14, 1025:13-17.) It is comparable in potency to codeine. (*Id.* at 1025:13-17.) An opioid is a drug that has been synthesized from material in the opium poppy and which binds to opioid receptors in the body in order to provide an analgesic response. (Smith,[11] Tr. 15:3-6.)

12. Tramadol has been used to treat moderate to severe pain for many years. ('887 patent, 1:12-23.) It was first synthesized in the early 1960s and was made available for pain treatment in Germany beginning in the late 1970s in immediate release forms. (Grond, Tr. 1023:16-1025:6; Smith, Tr. 12:11-22.) Although tramadol

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[9]The '430 patent is a continuation of the '887 patent. ('430 patent, cover page.) Thus, the specifications of the two patents are substantially the same. *Transco Prods. Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 555-56 (Fed. Cir. 1994). For simplicity, specification references will be made to the '887 patent.

[10]Dr. Stefan Grond is a physician specializing in anesthesia and pain management at Hospital Lippe in Detmold, Germany, and a professor of anesthesia at the Medical University of Hannover in Hannover, Germany. (Grond, Tr. 963:3-18.)

[11]Dr. Kevin J. Smith is Head of Clinical Pharmacy in Europe for Mundipharma GmbH ("Mundipharma"). (Smith, Tr. 8:4-11.) Smith is a named inventor of the patents-in-suit. Mundipharma is a German company that shares a common owner with, but is otherwise independent from, Purdue and Napp. (*Id.* at 11:1-4.)

was patented in the United States in 1972 by Grünenthal GmbH ("Grünenthal"), it was not widely available for patient use outside of Germany until the mid-1990s. (Defendants' Trial Exhibit ["DTX"]-458; Kaiko,[12] Tr. 209:2-4; Smith, Tr. 12:18-13:4.) Tramadol was not added to the World Health Organization ("WHO") guidelines for cancer pain management until 1996. (Grond, Tr. 1051:14-16; Smith, Tr. 13:5-16:7; PTX-557 at 18-19, 50-51.)

13. Tramadol has the chemical name (+)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol ('887 patent, 1:10-12), which explains the need for a good nickname like "tramadol." The drug is a racemic compound, in other words a 50%-50% mixture of two compounds that have identical chemical formulas but are mirror images of each other. (Weinberger,[13] Tr. 858:1-6; Grond, Tr. 983:8-22, 987:22-988:15.) Each of the two compounds is called an enantiomer and is given the designation of either (+) or (-); each compound has a different mechanism of action similar to that of antidepressents. (Weinberger, Tr. 858:1-5, 859:21-23; Grond, Tr. 983:8-984:14, 987:22-988:15.) The compound (+)-tramadol acts mainly in the spinal cord as a seratonin reuptake inhibitor. (Weinberger, Tr. 859:21-860:8; Grond, Tr. 986:4-10.) The compound (–)-tramadol also works in the spinal column but as a norepinephrine reuptake inhibitor. (Weinberger, Tr. 859:22-23; Grond, Tr. 986:11-12.) Both seratonin and norepinephrine are neurotransmitters, and blocking their reuptake

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[12]Dr. Robert F. Kaiko is the Vice President of Research and Development for Portfolio Development at Purdue. (Kaiko, Tr. 204:7-10.)

[13]Dr. Michael Weinberger is a physician and the Director of the Pain Service and the Palliative Care Service at Columbia University Medical Center, New York Presbyterian Hospital. (Weinberger, Tr. 835:15-20.)

inhibits the transmission of pain sensations. (Weinberger, Tr. 859:21-860:8.) Both (+)-tramadol and (–)-tramadol are metabolized by the liver into metabolites, at least one of which, the M_1 metabolite, is important to the effect of the drug. (Weinberger, Tr. 858:10-859:20.) The M_1 metabolite has activity at the μ opioid receptor, similar to morphine. (*Id.*)

14. All three mechanisms — (+)-tramadol, (–)-tramadol, and the M_1 metabolite — add together to produce analgesia. (*Id.* at Tr. 859:15-860:8.) All of them work in the central nervous system and must therefore cross the blood-brain barrier, a physiological barrier that prevents certain materials in the blood from entering the brain and the spinal cord. (Grond, Tr. 984:19-987:11.)

15. In part because of the complexity of the drug, there is no established blood plasma level above which tramadol can be expected to provide analgesia in the average patient. (Smith, Tr. 19:10-21:9; Grond, Tr. 985:8-987:21.) In other words, a minimum effective concentration ("MEC") for tramadol has not been thoroughly established. (Smith, Tr. 19:10-21:9; Grond, Tr. 987:3-993:3; 1036:3-1037:4.) For that reason, it is, and was at the time of the filing of the application for the parent to the patents-in-suit, more difficult to estimate the analgesic effect of tramadol than other opioids, such as fentanyl, morphine, hydromorphone, and oxycodone. (Grond, Tr. 1028:18-1029:10.) Nonetheless, a relationship is known to exist between the concentration of tramadol in a patient's blood and the pain relief experienced by that patient. (Weinberger, Tr. 885:20-887:8, 922:19-923:11; Katz,[14] Tr. 621:9-622:8.) The

[14]Dr. Warren A. Katz is a rheumatologist who has been practicing medicine for more than 42 years. Dr. Katz teaches at the University of Pennsylvania through Penn

patents-in-suit describe tramadol formulations that preferably maintain a drug concentration in the blood "within the therapeutic range" for 12 hours or more.[15] ('887 patent, 1:38-40.)

ii. *Controlled Release Formulations*

16. Conventional release, or immediate release, preparations of tramadol are typically administered four to six times per day. ('887 patent, 1:12-18; Grond, Tr. at 1048:12-20; PTX-844 at 3.) Controlled release preparations, in contrast, achieve a slow release of a drug over an extended period of time. ('887 patent, 1:34-36.) The patents-in-suit are directed to controlled release preparations of tramadol that are to be taken one or two times daily. (*Id.* at 1:23-25.)

17. Controlled release delivery systems are known to offer advantages over conventional dosage forms, including increased patient compliance with prescriptions, decreased total drug delivery, and decreased side effects. (DTX-107 at 5; Palmieri,[16] Tr. 1267:25-1268:20.) Those advantages were well known as early as 1980, when one of the inventors of the patents-in-suit, Stewart Leslie, published an article entitled "Continus Controlled Release Preparations" (the "Leslie article"), which describes the benefits of controlled release dosage forms.[17] (DTX-107.) More particularly, the Leslie

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Presbyterian Medical Center, where he was Chief of Rheumatology for approximately 14 years. (Katz, Tr. 474:4-479:7.)

[15]The mentioned "therapeutic range" is not defined in the patent.

[16]Dr. Anthony Palmieri, III, is Clinical Assistant Professor of Pharmaceutics at the University of Florida, College of Pharmacy. (Palmieri, Tr. 1246:13-18.)

[17]The named inventors on the patents-in-suit are the same. They are Ronald Brown Miller, Stewart Thomas Leslie, Sandra Therese Antoinette Malkowska, Kevin

article detailed the advantages of a specific system or template for formulating controlled release drugs. The system, known as the Continus® ("Continus") controlled release system, was used by Napp researchers beginning in the 1980s. (DTX-107 at 1, 7.) Plaintiffs acknowledge that Leslie obtained a U.S. patent on the Continus system, No. 3,965,256, which issued on June 22, 1976. (D.I. 334[18] at ¶ 122; DTX-302.) The patents-in-suit employ the Continus controlled release system. (Miller,[19] Tr. 1233:24-1234:2, 1241:15-18.)

18. Controlled release oral dosage forms are made with excipients (i.e., inert ingredients) that have certain chemical characteristics. (Palmieri, Tr. 1289:13-22, 1287:11-1288:14, 1291:14-1291:25, 1298:12-16; DTX-839.) Pharmaceutical formulators have been manipulating mixtures, structures, and coatings to make controlled release dose forms since 1955. (Palmieri, Tr. 1286:14-20.) Commercial controlled release products began to appear on the market in the United States in 1960. (*Id.* at 1286:21-1287:10.) Basic textbooks such as *Introduction to Pharmaceutical Dosage Forms* (1981) describe "delayed action dosage forms," (DTX-476 at 390; Palmieri, Tr. 1290:13-1291:7), and textbooks such as the *Handbook of Pharmaceutical Excipients* (1986) describe excipients appropriate for controlled release formulations.

John Smith, Walter Wimmer, Horst Winkler, Udo Hahn, and Derek Allan Prater. Accordingly, whenever this opinion refers to an individual as an inventor or a co-inventor, it should be understood to mean that the individual is an inventor of both of the patents-in-suit.

[18]D.I. 334 is Plaintiffs' corrected proposed findings of fact and conclusions of law.

[19]Dr. Ronald Miller is an inventor of the patents-in-suit and was Managing Director of the Research & Development Division at Napp from 1994 to 1997. (Miller, Tr. 1232:3-18.)

(DTX-839; Palmieri, Tr. 1288:6-1289:25.) Examples of oral controlled release delivery systems include permeable coatings (Palmieri, Tr. 1264:5-13), controlled release matrices surrounded by cosmetic coatings (*id.* at 1265:2-15), and osmotic pumps that use semi-permeable coatings (*id.* at 1265:25-1266:11).

19. The Leslie article explains that controlled release delivery systems generally rely on at least one of four general principles: osmotic pressure, ion exchange, dissolution, and diffusion. (DTX-107 at 6.) The Continus system uses dissolution and diffusion. (*Id.* at 7.) "Dissolution" is a reference to the water solubility of the drug and/or the coating as a means to control the delivery of the drug. (*Id.*) For example, a salt formation can decrease the solubility of a drug with an otherwise high dissolution rate, making it more suitable for use in a controlled release formulation. (*Id.*) "Diffusion" refers to the movement of drug molecules from a region of high concentration to one of lower concentration, through a water insoluble polymer, for example, again as a means of controlling drug delivery. (*Id*; Palmieri, Tr. 1264:5-13.) The Leslie article teaches that the Continus system may be used to realize diffusion and dissolution over a period of 12 hours *in vivo*, and it provides a sample *in vitro* dissolution rate for a tablet, with aminophylline as the active ingredient, that is controlled to give even release over a period of six hours. (DTX-107 at 7-8.)

20. Through routine experimentation, a formulator can substitute a different active ingredient with a similar physical chemical profile into a once-a-day controlled release formulation and produce a formulation that has a dissolution rate similar to the original formulation. (Palmieri, Tr. 1287:11-1288:5; DTX-107 at 7.) Par's formulation

expert, Dr. Anthony Palmieri, testified that, in order to make a once-a-day dose formulation using a given active ingredient, a formulator would start by evaluating controlled release forms that have active ingredients with similar physical chemical profiles, prepare prototype formulations with reference to the list of excipients that were available, and do dissolution work to optimize the formulation using "routine ordinary quite frankly often dull laboratory experiments." (Palmieri, Tr. 1255:24-1256:2, 1287:11-1288:5.) For example, Dr. Palmieri testified that a formulator could decrease or increase the thickness of the coating or use different excipients to obtain the desired controlled release profile. (*Id.* at 1323:21-1324:15.) The Leslie article also explained that, by varying the amounts of the different excipients used, "it is possible to vary the rate of drug diffusion through the matrix and subsequent rate of dissolution."[20] (DTX-107 at 7.) A formulator would then interact with clinicians through an iterative process to tweak the dose form if needed. (Palmieri, Tr. 1292:1-13, 1323:21-1324:6.) In rebuttal, Plaintiffs' expert testified that a formulator "couldn't expect to simply transpose one drug for another into a pharmaceutical[] controlled release formulation and expect to achieve the same dissolution profile, the same pharmacokinetic data and, of course,

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[20]Specifically, the Leslie article teaches the following:

> By varying either: the amount of cellulose; the degree of cellulosic hydration; the amount of higher aliphatic alcohol utilised; the ratio of cellulose to higher aliphatic alcohol; or the ratio of water soluble to water insoluble cellulose, it is possible to vary the rate of drug diffusion through the matrix and subsequent rate of dissolution.

(DTX-107 at 7.)

the same pharmacodynamic data."[21] (Davies,[22] Tr. 1489:16-23.) But Plaintiffs failed to address Par's main point: the alterations that are needed to achieve a successful controlled release formulation would be the result of routine experimentation.

21. The patents-in-suit describe controlled release matrices as preferred embodiments for the claimed controlled release tramadol, along with suitable excipients for inclusion in such matrices. ('887 patent, 3:39-68.) Normal release matrices having a coating that provides for controlled release of tramadol are also described, along with suitable excipients. ('887 patent, 3:45-47, 4:24-55.) It is undisputed that Par's tablets have a controlled release coating over a normal release matrix, rather than a controlled release matrix. (Uncontroverted Facts, D.I. 326 at ¶ III.B.(25); Davies, Tr. 661:10-20; PTX-166 at PAR015917.)

iii. *Plaintiffs' Development of the Claimed Inventions*

22. Before detailing the development of the claimed inventions, it will be helpful to define some terms used in the art to characterize the properties of drugs and drug formulations. As noted earlier, the "minimum effective concentration" of a therapeutic drug, or "MEC," is the minimum amount of drug per unit volume of blood plasma needed to provide a therapeutic effect in the average patient. (Findings of Fact

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[21]Pharmacokinetic ("PK") data refers to data that measures the physical disposition of a drug in the body (e.g., absorption rate). *Stedman's Medical Dictionary* at 1473 (28th ed. 2006) ("*Stedman's*"). Pharmacodynamic data refers to data that measures a drug's action (e.g., therapeutic effect). *Id.* at 1472.

[22]Dr. Martyn C. Davies is a professor of formulation science, physical pharmaceutics, and drug delivery controlled release technology at the School of Pharmacy at the University of Nottingham in Nottingham, England. (Davies, Tr. 651:6-52:3.)

["FF"] ¶ 15.) "Onset of action" is the time at which a drug formulation begins to provide a therapeutic effect. (Davies, Tr. 695:10-697:1.) Plaintiffs use the term "onset concentration" to mean the blood plasma level of a drug at the onset of action. (D.I. 331[23] at 15-16.) For convenience, I will use that term as well. As used at trial, the term "trough concentration" refers to the blood plasma level of a drug at the end of a dosing interval. (Grond, Tr. 1056:4-24.) "Steady state" refers to the point at which the average blood plasma level over a dosing interval does not change with each successive dose. *See Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 98 F. Supp. 2d 362, 373-76 (S.D.N.Y. 2000). "C_{max}" refers to the peak blood plasma level of a drug following administration, and "W_{50}" is the duration of time over which the plasma concentrations are equal to or greater than 50% of C_{max}. (D.I. 247[24] at 10.) "T_{max}" is the time it takes to get to C_{max}. (Palmieri, Tr. 1314:23-1315:5.)

23. Scientists at Napp, including Smith, were involved in the development of a twice-a-day tramadol preparation in the early 1990s. (Smith, Tr. 12:3-10.) In August 1991, Dr. Derek Prater, a director of technical development at Mundipharma Research Ltd. ("Mundipharma Research") and a named inventor of the patents-in-suit, suggested that, based on data obtained during the twice-a-day development, Smith should look into a once-a-day formulation. (Prater, Tr. 82:5-83:6; PTX-50 at NAPP0342385.)

24. In April 1992, Smith calculated theoretical dissolution rates and blood plasma profiles for a once-daily formulation. Smith's calculations were based, in part,

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[23]D.I. 331 is Plaintiffs' post-trial brief.

[24]D.I. 247 is the parties' joint claim construction chart.

on a published 1986 paper by Dr. W. Lintz, et al., entitled "Bioavailability of Enteral Tramadol Formulations" ("Lintz"), which evaluated an oral immediate release preparation of tramadol. Smith relied on the MEC assumed in Lintz, which was 100 ng/ml. (Smith, Tr. 18:5-26:21; PTX-594 at NAPP0041240-41; PTX-42 at NAPP0096248.) Lintz also reported that tramadol has good water solubility, is rapidly absorbed, has a long half-life, and has high bioavailability relative to other centrally acting analgesics.[25] (PTX-594 at NAPP0041240, NAPP0041245.) Thus, Lintz concluded that "the duration of analgesia of tramadol is likely to be longer with equianalgesic doses and equal pain intensity than that of pentazocine and codeine."[26] (PTX-594 at NAPP0041245.)

25. Smith disclosed his calculated theoretical dissolution rates and blood plasma profiles in a memo to Leslie and Prater dated April 24, 1992. (PTX-42.) To calculate his theoretical data Smith used the "favourabl[e]" elimination half-life that had been reported for tramadol, along with the high bioavailability, and determined the rate at which tramadol would need to enter the blood stream in order to maintain a plasma concentration above the 100 ng/ml level for 24 hours. (*Id.* at NAPP0096248-49.) After discussing his calculations, Smith concluded that "albeit at an early (and purely

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[25]Bioavailability is the proportion of an administered dose that is absorbed into the bloodstream. *Stedman's* at 219. Active ingredients with good bioavailability were known at the time to be good candidates for controlled release dose forms. (Palmieri, Tr. 1292:14-1294:7.)

[26]"Equianalgesic" means "having the same analgesic effect as a given dose of another analgesic agent." *Dorland's Illustrated Medical Dictionary* at 646 (31st ed. 2007).

theoretical) stage, I think we can be hopeful that a once-a-day preparation is a realistic target." (*Id.* at NAPP0096249.)

26. In late 1993, formulators supervised by Prater and co-inventor Sandra Malkowska, the Assistant Director of Formulation Laboratories at Napp, created a once-daily tramadol formulation using Smith's theoretical release data. Napp formulators chose hydrogenated vegetable oil ("HVO") to slow the dissolution rate after trying and rejecting several other waxes. They made and tested tablets containing different ratios of tramadol to HVO and determined that an equal amount of tramadol hydrochloride ("tramadol Hcl") and HVO seemed most promising for a once-daily formulation that would also be suitable in size for patients to swallow.[27] (Malkowska Tr. 1064:3-10, 1160:3-61:2; Prater Tr. 79:3-13, 84:6-86:25, 92:3-93:22; PTX-71 at NAPP0096234; PTX-69 at NAPP0371891 [F474/07], NAPP0371895 [F474/15], NAPP0371903 [F474/30].)

27. In March 1994, Smith supervised TRAM.PKIN4, the first PK pilot study on the once-daily formulation that Prater and Malkowska had developed. TRAM.PKIN4 was a single dose study that compared blood plasma levels produced by 200 mg of the Napp controlled release formulation to a single 100 mg dose of a commercial immediate release tramadol formulation. As Smith explained, a once-daily dose of 200 mg is comparable to 50 mg of an immediate release dose taken four times daily, which is a typical dosing regimen for immediate release tramadol that was known to provide

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[27]Tramadol Hcl is a salt of tramadol. (Uncontroverted Facts, D.I. 326 at ¶ III.B.(24).)

pain relief.[28] (Smith, Tr. 27:3-35:2, 73:4-15; Katz, Tr. 500:2-506:9, 512:17-513:18; Grond, Tr. 1048:15-20, 1051:14-25; PTX-844 at 3.) Accordingly, Smith compared the plasma levels of the Napp controlled release formulation to one-half the plasma levels of the 100 mg immediate release control dose, i.e., the plasma levels that would be achieved by a 50 mg dose. TRAM.PKIN4 showed that the Napp controlled release formulation maintained plasma concentrations for more than 24 hours above the six-hour trough concentration, i.e., a trough concentration occurring at six hours after administration of a 50 mg dose. That gave Smith confidence that Napp had successfully made a once-daily formulation. (Smith Tr. 27:3-37:5; PTX-18 at NAPP0093094-95, NAPP0093111; Grond Tr. 1056:4-25.)

28. TRAM.PKIN4 also showed that the W_{50} of the controlled release formulation was greater than the W_{50} for the immediate release formulation. Smith took that larger W_{50} to mean that the controlled delivery of the formulation was "very strong." (Smith Tr. 38:7-40:11; PTX-18 at NAPP0093103.)

29. The TRAM.PKIN4 study and its results were included as Example 8 and Figure 2 in the specifications of the patents-in-suit. ('887 patent, Fig. 2, 11:35-12:14; Weinberger, Tr. 917:4-16; Smith, Tr. 47:2-20.)

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[28]Both sides adopted the concept of dose proportionality with respect to the dosage levels of tramadol at issue in this case. Plaintiffs' pharmacokinetic expert testified that "[t]ramadol is dose proportional in the 100 to 400-miligram range, so the higher the dose, the higher the pharmacokinetic profile." (Davies, Tr. 708:5-7.) Smith believed that halving the plasma levels of the 100 mg immediate release dose would give the plasma levels that would be achieved by a 50 mg dose. (Smith, Tr. 32:21-34:13.) And Par's expert acknowledged that plasma concentrations of tramadol increase linearly over a dosage range of 50 to 400 mg. (Grond, Tr. 1028:3-5.)

30. Ronald Miller, one of the inventors of the patents-in-suit and the person to whom another inventor, Leslie, reported, testified that, when development began, he expected to successfully create a controlled release formulation of tramadol. (Miller, Tr. 1232:24-25, 1237:1-5.) Napp scientists used the Continus system to develop their controlled release formulation of tramadol (FF ¶ 17) because they believed that it was "reliable" and that it would lead to a successful result. (Miller, Tr. 1236:11-25, 1237:15-1238:12.) That belief was well founded. Napp had used the Continus system to develop various controlled release drugs at Napp for at least six different therapeutic indications. (*Id.* at 1233:24-1234:21.) Even with aminophylline, an active ingredient that was "an awkward substance to handle pharmaceutically," Napp had used the Continus system to achieve a controlled release formulation that is "highly effective" and "very stable." (Miller, Tr. 1234:22-1236:25.) Similarly, inventor Udo Hahn testified that he had no reason to think that tramadol could not be used with the Continus system. (Hahn, Tr. 1231:21-23.)

iv. *The Asserted Claims*

31. Plaintiffs are asserting claims 3, 13, 27, and 29 of the '887 patent and claims 5, 7, and 11 of the '430 patent. (D.I. 280.) Those claims all relate to controlled release oral formulations of tramadol suitable for dosing every 24 hours.

32. Specifically, the asserted claims of the '887 patent relate to preparations or tablets of tramadol, or its salt, that are covered by a controlled release coating made out of certain excipients, that have a certain dissolution rate under certain conditions when tested *in vitro* and that have various pharmacokinetic properties. ('887 patent,

12:50-64, 13:53-14:6, 16:1-5, 12-15; Smith, Tr. 23:21.) The claimed formulations are designed to provide pain relief for approximately 24 hours. ('887 patent, 12:32-34, 14:5-6.)

33. Claim 1 of the '887 patent, from which claim 3 depends, reads:

> A controlled release oral pharmaceutical preparation suitable for dosing every 24 hours comprising
> a substrate comprising a pharmaceutically effective amount of tramadol or a salt thereof;
> said substrate coated with a controlled release coating;
> said preparation having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0,1 N hydrochloric acid at 37° C. and using UV detection at 270 nm, between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, said preparation providing a therapeutic effect for about 24 hours after oral administration.

(*Id.* at 12:16-35.)

34. Dependent claim 3 provides narrower *in vitro* dissolution ranges than claim 1. (*Id.* at 12:50-64.) In other words, the range of dissolution percentages at certain time points is smaller. For example, claim 3 requires between 35% and 100% tramadol released after 8 hours, rather than the 10% to 100% called for in claim 1. (*Id.* at 12:62.)

35. Independent claim 13 claims a pharmaceutical "tablet" rather than a "preparation" and requires that the coated tablet provide "a W_{50} in the range of 10 to 33

hours when orally administered"; otherwise, claim 13 is identical to claim 1. (*Id.* at 13:53-14:6.)

36. Dependent claim 27 reads:

> A controlled release preparation in accordance with claim 1, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

(*Id.* at 16:1-5.)

37. Claim 29 is similar to claim 27 but depends from claim 13 rather than claim 1. (*Id.* at 16:12-16.)

38. The asserted claims of the '430 patent are similar to those asserted in the '887 patent but define the structure of the controlled release formulation with more detail.

39. Specifically, claim 1 of the '430 patent, from which the asserted claims depend, reads:

> A solid controlled release oral dosage form, comprising,
> a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a normal release matrix,
> said matrix overcoated with a controlled release coating comprising a polymethacrylate or a water insoluble cellulose,
> said dosage form providing a therapeutic effect for at least about 24 hours.

('430 patent, 12:41-51.)

40. With respect to the duration of therapeutic effect, the '887 patent uses the phrase "about 24 hours" and the '430 patent uses "at least about 24 hours." ('887 patent, 12:33; '430 patent, 12:49-50.) As will become apparent, the difference between those two phrases is irrelevant to the issues as I have decided them. Therefore, I will

simply refer to the duration of therapeutic effect required by all the asserted claims as "approximately 24 hours."

41. Claim 3, from which asserted claim 5 depends, requires the controlled release coating to comprise a water insoluble cellulose. ('430 patent, 12:54-57.) Claim 5 requires the controlled release coating to further comprise a polyvinylpyrrolidone. (*Id.* at 12:61-63.)

42. Claim 7 adds to claim 1 the same narrow *in vitro* dissolution rate as claim 3 of the '887 patent. (*Id.* at 13:1-12; '887 patent, 12:50-64.) Although claim 7 adds the term "about" to the dissolution ranges — claiming, for example, "about 0 to about 50% tramadol released after 1 hour" rather than the "0-50" provided in claim 3 of the '887 patent — that difference is immaterial to this case.

43. Claim 11 adds to claim 1 "a W_{50} in the range of 10 to 33 hours." ('430 patent, 14:11-12.)

D. *Therapeutic Effect of Par's Tablets*

44. Plaintiffs' infringement theory as to whether Par's tablets provide a therapeutic effect for approximately 24 hours relies on a comparison of the PK data of Ultram ER to a 50 mg dose of Ultram IR, the latter of which, Plaintiffs say, has an onset of action at 30 minutes. (D.I. 331 at 15-17; *see* FF ¶ 22.) Plaintiffs contend that, because the PK studies for Ultram ER reveal blood plasma concentrations of tramadol for approximately 24 hours above the onset concentration of 50 mg Ultram IR, and because Par's tablets and Ultram ER produce substantially similar PK values and are

"therapeutically equivalent," Par's tablets meet the 24-hour limitation in the asserted claims. (D.I. 331 at 18.)

45. Plaintiffs' theory requires me to make a number of factual findings, namely, whether 50 mg Ultram IR has an onset of action at 30 minutes, whether a dose of 50 mg Ultram IR can be used to measure the efficacy of Ultram ER, how the onset concentrations of Ultram IR compare to the blood plasma concentrations observed with Ultram ER, and the similarity of Ultram ER to Par's tablets.

i. *Bioequivalence of Ultram ER and Par's Tablets*

46. Taking the last issue first, I find that the therapeutic effect of Par's tablets will be the same as that provided by Ultram ER. Indeed, Par readily concedes this point: "Par's product will have the same efficacy as Ultram ER because its PK profile is the same throughout the entire curve ... ." (D.I. 337[29] at 4; *see* PTX-214 at PAR011462-66; Davies, Tr. 681:16-83:11; Weinberger, Tr. 841:8-17, 873:17-76:17; Grond, Tr. 997:6-21, 1000:3-8; PTX-166 at PAR015918; Elvin,[30] Tr. 452:10-54:14; Katz Tr. 517:23-18:8.) Thus, a demonstration of the therapeutic effect of Ultram ER is necessarily a demonstration of the therapeutic effect of Par's tablets.

ii. *Ultram IR*

47. Moving to the therapeutic effect of Ultram IR, I find for the following reasons that 50 mg Ultram IR provides a therapeutic effect and that onset of action of that dose occurs at 30 mintues.

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[29]D.I. 337 is Par's post-trial reply brief.

[30]Dr. Alfred Elvin is Par's Director of Biopharmaceutics. (Elvin, Tr. at 450:12-15; D.I. 326, Ex. E at 7.)

48. Plaintiffs' clinical expert, Dr. Warren Katz, testified that, in his experience prescribing Ultram IR to thousands of patients since the product was released in 1995, many of his patients tell him that they have at least some pain relief within the first 30 to 60 minutes of taking a 50 mg pill. (Katz, Tr. 491:9-492:23.) In line with that testimony, Dr. Katz published a peer-reviewed article in 1996 that reported that the onset of action following administration of 50 mg of Ultram IR occurred within one hour. (PTX-857 at 39; Katz, Tr. 495:7-497:7.) Dr. Katz also highlighted another article from the same journal (the "Lee article") that reported that an additional dose of 50 mg immediate release tramadol may be given if pain relief is inadequate at 30 to 60 minutes after the first dose. (PTX-858 at 336; Katz, Tr. 497:12-499:18.) From that statement, Dr. Katz reasonably surmised that some patients did have an adequate response to the first dose of tramadol in 30 minutes. (Katz, Tr. 498:19-24.)

49. Clinical studies support Dr. Katz's testimony. The NDA for Ultram IR contained twenty single dose pain trials. (PTX-883 at BVF00022012; Davies, Tr. 695:1-698:8; Grond, Tr. 1016:14-17:14.) Twelve of those twenty studies investigated the 50 mg dose of Ultram IR, six in dental pain models and six in surgical pain models. (PTX-883 at BVF00022012-16.) In ten of those twelve studies, 50 mg Ultram IR produced a mean onset of pain relief in about 30 minutes. Specifically, mean onset of action was 22 minutes in the 6-hour dental study TE/TE2 (*id.* at BVF00022029); 38 minutes in the 6-hour dental study TF (*id.* at BVF00022036); 30 minutes in the 6-hour dental study TG, (*id.* at BVF00022050); 24 minutes in the 8-hour dental study TH (*id.* at BVF00022057); 37 minutes in the 8-hour dental study TI (*id.* at BVF00022064); 21 minutes in the 8-hour

post-surgical study TA (*id.* at BVF00022100); 20 minutes in the 6-hour post-surgical study TC (*id.* at BVF00022107); 19 minutes in the 6-hour post-surgical study TJ (no placebo) (*id.* at BVF00022114); 36 minutes in the 6-hour post-surgical study TW (*id.* at BVF00022122); and 16 minutes in the 6-hour cesarean section study TV (*id.* at BVF00022166). Of the remaining two studies, one, TF3, had a mean onset of action of 62 minutes (*id.* at BVF00022043); and the results of the other, TB, were not analyzed due to insufficient enrollment (*id.* at BVF00022016). In an efficacy test sponsored by Purdue for a separate NDA, the median time to perceptible pain relief following administration of 50 mg Ultram IR was found to be 69 minutes (a mean time is not given); the median time to "meaningful pain relief" was found to be 3.1 hours. (Grond, Tr. 1046:16-1048:11, 1018:2-11.) Taking the reported summary from each of the analyzed studies, the average time to at least some pain relief was 33 minutes.

50. At trial, Par's expert, Dr. Stefan Grond, dismissed the significance of those clinical studies. Relying on a report from an FDA reviewer that concluded that tramadol 50 mg was "positive" in only one of eight of the trials (PTX-883 at BVF00022017; Grond, Tr. 1017:2-8), Dr. Grond testified that, "in my opinion, the FDA concluded ... that 50 mg of Tramadol immediate release has marginal efficacy, and in my opinion, you cannot take only one of eight studies and, using that, ... make an assumption of analgesic efficacy at between 30 minutes and six hours." (Grond, Tr. 1017:9-14.)

51. However, the FDA reviewer's conclusion on which Dr. Grond relies does not address onset of action. Although the clinical studies measured both pain intensity and pain relief (*e.g.*, PTX-833 at BVF00022025, 26), the FDA reviewer based his one-

of-eight conclusion on pain intensity measurements alone. Specifically, the FDA reviewer looked at the pain intensity differences from baseline ("PID"), measured after the first half hour and hourly thereafter, and summed those differences for the first three hours ("3-hour SPID"). (*Id.* at BVF00022012.) The reviewer considered a drug to be "positive" in a given study if the 3-hour SPID for the drug beat placebo. (*Id.* at BVF00022013-16.) In contrast to the 3-hour SPID measurements, the mean pain relief measurements show that 50 mg tramadol was greater than placebo at the first half hour in all but two of the studies. (*Id.* at BVF00022025, 32, 39, 46, 53, 60, 88, 96, 103, 118, 162.)

52. Furthermore, although Dr. Grond is clearly well-credentialed and a recognized authority in his field of anesthesia and pain management, I do not agree with him that the FDA endorsed a conclusion that a 50 mg dose was only marginally effective. To the contrary, the FDA approved the use of an initial 50 mg dose of Ultram IR for the American public where "rapid onset of analgesic effect is required." (PTX-844 at 3.) Apparently, the FDA did not require that 50 mg Ultram IR provide some pain relief in 30 minutes for all patients before deeming it effective, and there is no basis for me to hold Ultram IR to a more exacting efficacy standard than did the FDA. The Ultram IR label insert states, "Onset of analgesia in humans is evident within one hour after administration"; the FDA approved that label following the submission of the clinical studies. (PTX-844 at 3; PTX 883A at BVF00021883; Katz, Tr. 493:18-94:12; Davies, Tr. 685:9-20, 697:2-9, 698:9-14.) The FDA's approval, the clinical studies, Dr. Katz's clinical experience, Dr. Katz's article, and the Lee article that he referenced in his testimony (FF ¶ 48) all lead me to conclude that Plaintiffs have established, by a

preponderance of the evidence, that 50 mg Ultram IR can and frequently does provide an analgesic effect at 30 minutes after oral administration.

iii. *Bioequivalence of Ultram IR and Ultram ER*

53. Par disputes whether the FDA allowed Biovail[31] to rely on the efficacy of Ultram IR to establish the efficacy of Ultram ER, with the implication being that, if the FDA did not allow Biovail to do so, I should not allow Plaintiffs to do so either. (D.I. 337 at 4-5; D.I. 336[32] at 4 n.1.)

54. Biovail's Ultram ER NDA was submitted pursuant to § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (codified at 21 U.S.C. § 355(b)(2)) and relied on efficacy and safety data for Ultram IR. (Uncontroverted Facts, D.I. 326 at ¶ III.C.(31); PTX-879 at BVF00144032.) In its draft "Guidance for Industry," the FDA has stated that a 505(b)(2) application is appropriate for a controlled release product that is bioequivalent to a previously approved drug where "1. [t]he proposed product is at least as bioavailable as the approved pharmaceutically equivalent product ... or 2. [t]he pattern of release of the proposed product, although different, is at least as favorable as the approved pharmaceutically equivalent product." (DTX-479 at 6.)

55. Biovail initially sought FDA approval to market Ultram ER for the treatment of "moderate to moderately severe pain," which would encompass both chronic and acute pain. (PTX-833 at BVF00021887.) That was the same indication for which Ultram IR had been approved in 1995. (Weinberger Tr. 889:5-891:4; PTX-750 at

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[31]As noted earlier, Biovail is the holder of the NDA for Ultram ER. (FF ¶¶ 4, 6.)

[32]D.I. 336 is Plaintiffs' post-trial reply brief.

BVF00117572.) As a part of the Ultram ER approval process, Biovail submitted multiple clinical studies comparing the PK data for a single 200 mg Ultram ER tablet to data for a 50 mg Ultram IR dose taken four times a day at regular and at irregular intervals. (PTX-750 at BVF00117578-93.)

56. In October 2004, Biovail received an "approvable" letter from the FDA that identified questions about Biovail's proposed labeling and studies and stated that "upon review of the data presented in [the] NDA, [Ultram ER] is *not* bioequivalent to the reference listed product." (PTX-884 at BVF00529849 (emphasis added).) The letter requested an additional trial demonstrating "robust evidence of efficacy." (*Id.* at BVF00529850.) The FDA also issued two clinical reviews recommending that Biovail's NDA 21-692 not be approved, "based on lack of efficacy in conjunction with the high rate of adverse events." (DTX-354 at SBA 208; DTX-353 at SBA 134.)

57. On March 7, 2005, Biovail submitted a "Complete Response" letter to the FDA, in which Biovail limited the proposed indication for Ultram ER to "chronic pain" and submitted new analyses of its previously conducted clinical studies to explain how those studies revealed that Ultram ER was, indeed, bioequivalent to Ultram IR. (PTX 770 at BVF00160624, BVF00160636.) Biovail did not conduct additional clinical trials. (*Id.* at BVF00160630, BVF00160635.)

58. Following Biovail's response, the division director responsible for dealing with Biovail's NDA, Dr. Robert Rappaport, issued a "Division Director Review and Basis for Approval Action," in which he noted that he disagreed with the clinical review team and that he had concluded that Biovail had "provided adequate evidence of efficacy in

support of [its] marketing application for [Ultram ER]." (PTX-746 at SBA 49.) Following a review of Biovail's March 7 Complete Response, additional FDA reviewers concluded that, although there were still some questions as to the efficacy of Ultram ER at steady state, "the [bioequivalence] of [Ultram ER] to Ultram [IR] was demonstrated after [a] single daily dose in all [of Biovail's] studies." (DTX-356 at SBA 478.) Those reviewers, like Rappaport, concluded that Biovail's application was acceptable. (*Id.* at SBA 477.) The FDA ultimately approved Ultram ER, on September 8, 2005, and authorized it to be labeled for "moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time." (PTX-747 at BVF00190805, 816, 840.)

59. Based on the foregoing record, and contrary to Par's assertion, it appears that the FDA ultimately did conclude that the PK data submitted by Biovail was sufficient to establish bioequivalency. Although the FDA initially asked for direct clinical evidence of efficacy, it did not finally require more studies for approval. Par highlights Plaintiffs' statement in post-trial briefing that the FDA considered bioequivalence at steady state, rather than after an initial dose. (D.I. 337 at 5 n.1 (citing D.I. 331 at 14).) But that statement is not inconsistent with Plaintiffs' argument that PK data from Ultram IR can be used to measure the efficacy of Ultram ER. That Biovail only established bioequivalence as to steady state merely reflects the threshold showing that the FDA required for approval of Ultram ER for chronic pain. In other words, just because Biovail may not have needed to establish a single pill equivalency before the FDA does not mean that it could not have. In fact, quite the opposite appears to be true in light of the reviewer comments that "the [bioequivalence] of [Ultram ER] to Ultram [IR] *was*

demonstrated after [a] single daily dose in all [of Biovail's] studies." (DTX-356 at SBA 478 (emphasis added).)

60. I conclude that Plaintiffs have shown by a preponderance of the evidence that a single dose of 200 mg Ultram ER is bioequivalent to a 50 mg Ultram IR dose taken four times a day and that the efficacy of Ultram IR is a proper basis on which to judge the efficacy of Ultram ER.

iv. *Therapeutic Effect of Ultram ER*

61. Biovail's Study 2551, submitted as a part of its NDA, compared the PK profile of four 50 mg Ultram IR tablets taken every six hours to one 200 mg Ultram ER tablet. (Davies, Tr. 700:12-02:22; PTX-750 at BVF00117589-93). That study reveals a 30-minute blood plasma concentration for 50 mg Ultram IR of 40 ng/ml. (Davies, Tr. 703:23-04:19; PTX-750 at BVF00117590.) Plaintiffs' formulation expert, Dr. Martyn Davies, estimated that, based on the same study, a 200 mg dose of Ultram ER provided blood plasma concentrations above that 40 ng/ml level for about 32 hours. (Davies, Tr. 704:13-23; PTX-750 at BVF00117590; DTX-685 at BVF00123144.)

62. With respect to the 300 mg Ultram ER tablet, the plasma concentrations of tramadol will increase proportionally from the 200 mg Ultram ER tablet. (Grond, Tr. 1028:3-8.) Based on dose proportionality (*see supra* note 28), Dr. Davies determined that, because 200 mg Ultram ER is therapeutically effective for about 24 hours as shown by its plasma levels, the 300 mg Ultram ER tablet has at least the same duration of efficacy given its higher plasma levels. (Davies Tr. 707:5-708:11; PTX-750 at BVF00117609).

63. With respect to the 100 mg Ultram ER tablet, Dr. Davies relied on Biovail's single dose PK Study 2677, also submitted as a part of its NDA, to determine the duration of efficacy. Study 2677 graphed the blood plasma levels provided by a target formulation of 100 mg Ultram ER against those provided by a 100 mg Ultram IR control. Using Study 2677 and the 40 ng/ml onset concentration at 30 minutes from Study 2551 as a reference point, Dr. Davies determined that a 100 mg dose of Ultram ER maintains therapeutic plasma levels above that known therapeutic concentration for about 25 hours. (Davies Tr. 708:17-10:13; PTX-750 at BVF00117643; PTX-878 at BVF00127709.)

64. Par does not argue that the 30-minute onset concentration for 50 mg Ultram IR was inaccurately measured or that the various dosage strengths of Ultram ER fail to provide blood plasma concentrations above that concentration level for approximately 24 hours. Rather, its argument is pinned on the concept that onset of action for 50 mg Ultram IR does not occur at 30 minutes. I have rejected that position. (FF ¶ 52.) Par also vigorously disagrees with the general notion that 40 ng/ml represents an effective concentration of tramadol. However, as already discussed (FF ¶ 60), and as further explained in my Conclusions of Law ["CL"], *infra*, ¶¶ 8-12, I am persuaded that the 40 ng/ml blood plasma concentration is a proper marker at which the duration of therapeutic effect can begin to be measured. Thus, Plaintiffs have sufficiently established that the 100 mg, 200 mg, and 300 mg dosage strengths of Ultram ER—and, because of their bioequivalency to Ultram ER, the same dosage strengths of Par's tablets (FF ¶ 46)—provide a therapeutic effect for approximately 24 hours.

E. *Prosecution History of the Patents-in-Suit - Chapter I*

65. The prosecution history of the patents-in-suit is relevant to issues of both obviousness and inequitable conduct. At this point, I will discuss the portion of the prosecution history that relates most directly to the question of obviousness.

66. The application that issued as the '887 patent, Application No. 08/677,798 (the "'798 application"), was filed on July 10, 1996. ('887 patent, cover page.) The '798 application was filed as a division of Application No. 08/241,129 (the "'129 application"), which was filed May 10, 1994 and issued as U.S. Patent No. 5,591,452 (the "'452 patent") on January 7, 1997. ('452 patent, cover page.)

67. The application that issued as the '430 patent, Application No. 09/800,204 (the "'204 application"), was filed on March 6, 2001. ('430 patent, cover page.) The '204 application was filed as a continuation of the application for the '887 patent. (*Id.*)

68. The '887 patent and its parent, the '452 patent, claim priority to four foreign patent applications filed from May 10, 1993 to March 14, 1994. ('887 patent, cover page.) Under 35 U.S.C. § 119, the claims set forth in a United States application are entitled to the benefit of a foreign priority date if the corresponding foreign application provides a sufficient written description of what is claimed in the United States patent. *In re Gosteli*, 872 F.2d 1008, 1010-11 (Fed. Cir. 1989). The earliest of those claimed priority documents is German Patent Application No. DE 4315525 (the "German priority document"). (Uncontroverted Facts, D.I. 326 at ¶ III.G.(64).)

69. The German priority document does not disclose any PK data, any product having a 24-hour therapeutic effect, any of the dissolution ranges stated in the

asserted patents to be suitable for once daily administration, controlled release coatings of tablets suitable for once-a-day dosing, or any W_{50} values. (DTX-21; Grond, Tr. 997:22-998:20; Palmieri, Tr. 1271:22-73:12.) Moreover, PK study TRAM.PKIN4, which underlies Figure 2 and Example 8 of the patents-in-suit, was conducted in March 1994, almost a year after the filing of the German priority document. (FF ¶¶ 27-29.) Thus, I agree with Par (D.I. 339[33] at ¶ 240) that the asserted claims of the '887 patent are not supported in the German priority document and are not entitled to that document's May 10, 1993 filing date.[34]

70. Plaintiffs are silent as to whether the German document entitles them to a foreign priority date. However, they do not dispute that the references raised by Par are prior art. (*See* D.I. 331 at 27.)

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[33]D.I. 339 is Par's proposed findings of fact and conclusions of law.

[34]Although Par alleges that the '430 patent also claims priority to the German priority document (D.I. 339 at ¶ 19), no such claim is apparent from the face of the '430 patent. Moreover, the prosecution history for the '430 patent reveals that, while the applicants claimed priority based on the same foreign patent applications as they did with the '887 patent (PTX-5 at PUR1109739, 1110465), the examiner determined that the conditions for claiming foreign priority under § 119 were not met (*id.* at PUR1110461, 65). Although the examiner did not provide his reasons, the context of his conclusion provides further support for mine. The '430 patent was amended during prosecution so that all the claims that included a 12-hour therapeutic effect limitation were deleted. (*Compare id.* at PUR1110106-07 *with* PUR1110448.) Such claims, which might more readily find support in the foreign applications, are present in the '887 patent. (*E.g.*, '887 patent, 13:20-40.) Of course, this case gives me no reason to question whether any of the non-asserted claims of the '887 patent are entitled to the filing date of the German priority document.

i. *Background References*

71. The references described in this subsection were all before the U.S. Patent Office ("PTO") during the prosecution of the patents-in-suit. ('887 patent at p. 2; '430 patent at pp. 1-2.)

72. U.S. Patent No. 4,844,909 (the "'909 patent"), filed October 26, 1987 and issued July 4, 1989, discloses controlled release formulations of 1 to 100 mg of hydromorphone. (DTX-24 at cover page, 2:41-44; Palmieri, Tr. at 1308:11-1309:7.) The '909 patent provides dissolution release rates and plasma profiles (DTX-24 at 1:8-26; Palmieri, Tr. 1314:18-21); it describes a T_{max} (*see* FF ¶ 22) between 4 to 8 hours (DTX-24 at 2:11-16; Palmieri, Tr. 1314:18-1315:9); it describes water insoluble cellulose coatings, such as ethylcellulose coatings (DTX-24 at 4:42; Palmieri, Tr. 1315:11-15); and it describes a normal release matrix having a coating that controls the release of the drug (DTX-24 at 3:64-66). Hydromorphone has similar water solubility, molecular weight, and dose size as tramadol. (Palmieri, Tr. 1317:4-20.)

73. U.S. Patent No. 5,266,331 (the "'331 patent"), filed November 27, 1991 and issued November 30, 1993, discloses controlled release formulations of 1 to 50 mg of oxycodone. (DTX-22 at cover page, 2:46-48.) Even though the '331 and '909 patents specify different active ingredients, they both disclose the identical dissolution release rate profiles, which are within the ranges of the asserted claims. (Palmieri, Tr. 1316:5-22.)

74. U.S. Patent No. 5,286,493 (the "'493 patent"), filed January 27, 1992 and issued February 15, 1994, discloses controlled release compositions of a variety of

analgesics: hydromorphone, oxycodone, dihydrocodeine, codeine, dihydromorphine, morphine, buprenorphine, "and the like." (PTX-609 at 7:31-37.) The '493 patent discloses controlled release coatings (PTX-609 at 2:67-3:5), including Eudragit®, which is a polymethacrylate (Palmieri, Tr. 1317:23-1318:9); it discloses a dissolution profile within the claimed ranges (PTX-609 at 4:57-67; Palmieri, Tr. 1312:24-1314:11); and it describes a substrate covered by a controlled release coating (PTX-609 at 9:23-30).

ii. *The Merck/Bondi Reference*

75. On June 7, 2000, the PTO issued an office action rejecting the pending claims of the '887 patent as anticipated by or obvious in light of European Patent No. 147,780 (the "Merck/Bondi reference"). (PTX-2 at PUR1109663.)

76. The Merck/Bondi reference discloses using a polyvinyl alcohol ("PVA") coating, which is a water insoluble polymer, to control the release of active pharmaceutical ingredients. (DTX-16 at NAPP0045471; DTX-1456.) It lists tramadol as one of hundreds of possible agents that may be used with PVA coating. (*Id.* at NAPP0045468.) The possible agents in the Merck/Bondi reference are listed in 12 different classes identified by letters (a) through (l), each of which lists multiple agents within the class. (*Id.* at NAPP0045466-70.) Tramadol, which is an opioid analgesic, is listed in Merck/Bondi as a preferred agent, but is misclassified as one of about 60 different agents in the non-steroidal anti-inflammatory drug ("NSAID") class. (*Id.* at NAPP0045468; Palmieri, Tr. 1355:5-17, 1397:10-1400:8.) The reference discloses that the amount of PVA coating can range from 1% to 15% by weight of the entire drug delivery device, with 3% to 10% PVA preferred. (DTX-16 at NAPP0045471.) Sixty-four

different examples of controlled release formulations are disclosed in Merck/Bondi, using various active agents and different PVA concentrations. None of the 64 examples uses tramadol. (*Id.* at NAPP0045472-77.) Claim 2 of Merck/Bondi claims tramadol as one of twelve potential NSAID active ingredients, where the PVA coating constitutes from 2% to 5% of the composition weight. (*Id.* at NAPP0045478-79.)

iii. *Issuance of the Patents-in-Suit*

77. In the PTO's June 7, 2000 office action, the examiner stated that the Merck/Bondi reference teaches a slow releasing composition of tramadol and that "[a]ny differences are minor modifications and are obvious because a skilled artisan would be motivated to make minor changes ... in order to determine optimal conditions." (PTX-2 at PUR1109664.)

78. The examiner then held a personal interview with the applicants, after which the examiner noted that he "agreed that the large scope of listed compounds in [the Merck/Bondi reference] did not establish a prima facie case of obviousness." (PTX-2 at PUR1109665; Davidson,[35] Tr. 258:15-259:12.)

79. According to the applicants' subsequent submission to the PTO, the prior art before the examiner also was discussed during the interview and generally categorized as follows:

> (a) prior art directed to pharmaceutical formulations that list tramadol in a long list of possible drugs to be included in such formulations but do not exemplify any tramadol formulations, namely the [Merck/Bondi reference] relied upon by the Examiner in the last Office Action; (b) prior art directed to controlled release

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[35]Clifford Davidson is Plaintiffs' U.S. patent prosecution counsel. (Davidson, Tr. 236:18-238:5.)

> formulations of narcotic opioid analgesics ...; and (c) prior art patents directed to controlled release formulation technology (where tramadol was not mentioned) and their applicability to the claimed invention.

(PTX-2 at PUR1109672.)

80. The '798 application matured into the '887 patent, which issued on July 3, 2001. ('887 patent, cover page.)

81. The '204 application, which ultimately issued as the '430 patent, was filed on March 6, 2001. ('430 patent, cover page.)

82. The same primary examiner reviewed both the '798 application and the '204 application. ('887 patent, cover page; '430 patent, cover page.) On April 23, 2002, after the '887 patent had issued, the examiner rejected the pending claims in the '204 application, stating that it would have been obvious to use the controlled release method taught in the Merck/Bondi reference for making an oral composition of tramadol. (PTX-5 at PUR1110001-1110002.) The examiner noted that "[t]he claims drawn to specific amounts, specific dosage forms, specific dissolution rates etc., are all obvious since a skilled artisan would reasonably be expected to tweak the controlled release form of tramadol to meet a variety of needs." (*Id.* at PUR1110002.)

83. In response, the applicants argued that one skilled in the art would not be motivated to select tramadol from the large number of active ingredients disclosed in the Merck/Bondi reference. (*Id.* at PUR1110110.) They also argued that the prior art did not teach the "24 hour therapeutic effect" limitation of the asserted claims. (*Id.* at PUR1110112-15.)

84. The examiner maintained his rejection until the applicants amended the claims to limit the claimed "controlled release coating" to one "comprising a polymethacrylate or a water insoluble cellulose." (*Id.* at PUR1110125, PUR1110145, PUR1110416.) The applicants argued that the Merck/Bondi reference did not disclose such a controlled release coating. (*Id.* at PUR1110416.) The claims were then allowed, subject to a terminal disclaimer with respect to the '887 patent. *See In re Goodman*, 11 F.3d 1046, 1052 (Fed. Cir. 1993) ("To prevent extension of the patent right beyond statutory limits, the doctrine of obviousness-type double patenting rejects application claims to subject matter different but not patentably distinct from the subject matter claimed in a prior patent."); 37 CFR 1.321(c) (specifying procedures for disclaiming the portion of the patent term following the expiration of a commonly owned patent that fits the description provided by *In re Goodman*).

85. The '430 patent issued on July 11, 2006. ('430 patent, cover page.)

F. *References Not Before the PTO*

i. *U.S. Patent No. 5,580,578 ("Oshlack")*

86. Benjamin Oshlack, former Vice President of Pharmaceutics at Purdue, is an inventor of U.S. Patent No. 5,580,578 (the "'578 patent" or "Oshlack"), filed July 27, 1993, as a continuation in part of the application for the '493 patent (*see* FF ¶ 74) and issued December 3, 1996. (Oshlack, Tr. 171:7-21, 189:16-19.) Oshlack is directed to a method of increasing the shelf life of solid controlled release formulations. (PTX-601 at 3:3-41; Oshlack, Tr. 186:18-187:10, 189:12-21.) Oshlack teaches that an increased

shelf life can be obtained by curing (heating) the controlled release formulation for an extended period. (PTX-601 at 3:41-64; Oshlack, Tr. 186:18-187:10.)

87. Oshlack describes various controlled release oral dosage formulations that are even closer to the asserted claims than is Merck/Bondi. Oshlack discloses specific examples of controlled release formulations that use morphine, hydromorphone, and acetaminophen as the active ingredients, but the reference broadly claims that it is applicable to controlled release dosage forms containing "systemically active therapeutic agent[s]." (PTX-601 at 20:12-39:26, 43:48-44:19; Oshlack, Tr. 187:17-24, 190:4-14.) Tramadol is claimed as one of 14 different "opioid analgesics" that qualify as appropriate therapeutic agents. (PTX-601 at 44:10-19, 29-36.)

88. Oshlack further describes controlled release coatings comprising either hydrophobic (water-insoluble) acrylic polymers (PTX-601 at 7:37-39) or polymethacrylates such as Eudragit® (*Id.* at 9:30-41; Palmieri, Tr. 1318:1-12, 1336:24-1337:7).

89. Claim 43 of Oshlack ("Claim 43") describes a dissolution profile through eight hours that falls within the ranges described in claim 1 of the '887 patent. The Claim 43 dissolution profile falls within the ranges of claim 3 of the '887 patent and claim 7 of the '430 patent for the first four hours and overlaps with the range given at eight hours for those same claims. (PTX-601 at 43:57-44:9.) The dissolution conditions described in Claim 43, the USP paddle or basket method at 100 rpm at 900 ml aqueous buffer at 37°C, are not the exact same conditions laid out in the asserted

claims of the patents-in-suit (which are based on the European method), but the differences are slight and usually do not produce significantly different results. (Palmieri, Tr. 1329:7-24.) Examples 19 and 20 of Oshlack, which use morphine, have dissolution results up to 14 hours that indicate that the dissolution rates are within the narrowest of the asserted claims of the patents-in-suit through 24 hours. (PTX-601 at 37:1-12.)

90. Oshlack claims that the formulations, including those that use tramadol as the active ingredient, provide "effective blood levels of [the] systemically active therapeutic agent for about 24 hours." (*Id.* at 44:8-9.) Although the Oshlack patent describes certain formulations in the examples as potentially being "suitable for once-a-day administration," none of those formulations involve tramadol. (*Id.* at 34:48-58, 36:1-2, 37:30-32, 45:20-21.)

91. Oshlack does not disclose a W_{50} value or a coating comprising polyvinylpyrrolidone.

ii. *U.S. Patent No. 5,478,577 ("Kaiko")*

92. Dr. Robert Kaiko, a Purdue scientist (Kaiko, Tr. 204:7-10.), is one of the named inventors of U.S. Patent No. 5,478,577 (the "'577 patent" or "Kaiko"), filed November 23, 1993, and issued December 26, 1995. (PTX-600.) Kaiko discloses 24-hour oral opioid formulations that provide "an initially more rapid opioid release" followed by sustained release of the drug later in the dosing interval but with significant fluctuation. (PTX-600 abstract; Kaiko, Tr. 219:12-220:13.) Kaiko discloses sustained

release formulations that include an effective amount of opioid in immediate release form in order to shorten T_{max}. (PTX-600 at 6:26-36; *see* FF ¶ 22.)

93. Kaiko discloses tramadol as one of more than 70 opioid analgesic compounds that may be used. (PTX-600 at 6:62-7:17). However, tramadol is not listed as a preferred opioid analgesic, and the examples all use morphine as the active ingredient, with an immediate release morphine coating. (*Id.* at 7:16-20, 13:45-24:5.) At least three of those examples have dissolution profiles for morphine that fall within the claimed ranges using the USP Apparatus II (Paddle Method) at 100 rpm and 37°C in simulated gastric fluid. (*Id.* at 14:46-67, 21:13-34.)

94. Kaiko claims that, in general, the disclosed controlled release formulations provide effective pain relief for "at least about 24 hours when administered to a human patient." (*Id.* at 24:18-20.) The patent also generally discloses a dosage form that is suitable for once-a-day administration. (*Id.* at 3:48-53.)

95. The reference describes coatings such as acrylic polymers, cellulosic materials, or a water insoluble wax. (*Id.* at 8:1-9:11, 13:18-21.) Specifically, the patent describes controlled release coatings comprising either polymethacrylate (*id.* at 8:29) or ethylcellulose, a water insoluble cellulose (*id.* at 9:4-11).

96. Neither the Oshlack reference nor the Kaiko reference, both of which were filed after the filing date of the German priority document, was included in the list of documents considered by the PTO during prosecution of the patents-in-suit. ('887 patent at pp. 1-2; '430 patent at pp. 1-2.)

G. *Commercial Success of Ultram ER*

97. Ultram ER was launched in the United States in 2006. (Rausser,[36] Tr. 783:20-23.) It is not unusual for expenses to exceed revenues for a new product during a product launch, and Ultram ER did not become profitable until 2008. (Axenroth,[37] Tr. 411:21-412:6.)

98. The parties dispute how the market for Ultram ER should be defined, but, under either side's market definition, Ultram ER has attained no more than half of a percent of total prescriptions of the relevant market for pain medications. (Rausser, Tr. 804:7-805:6; DTX-1201-01 to 1201-06.) A partial explanation for the low market share is significant generic competition by medications for moderate to moderately severe chronic pain, which is only a subset of the types of pain for which medication is available. Another partial explanation is Ultram ER's "Tier 3" formulary status, which carries with it a high "co-pay" for patients purchasing the medication.[38] (Axenroth, Tr. 398:22-404:15, 410:3-411:4.)

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[36]Dr. Gordon Rausser is the Robert Gordon Sproul Distinguished Professor of Economics at the University of California at Berkeley. (Rausser, Tr. 763:20-764:3.)

[37]Robert Axenroth is employed by Ortho as Group Product Director for Ultram ER. (Axenroth, Tr. 387:25-388:21.)

[38]A formulary lists drugs that managed care companies would have patients purchase, in order of preference. (Axenroth, Tr. 410:3-6.) Typically, there are three tiers in a managed care formulary: Tier I, Tier II, and Tier III. (*Id.* at 410:7-9.) Tier I usually contains generic products; Tier II usually contains preferred branded products; and Tier III usually contains non-preferred branded products. (*Id.* at 410:10-15.) That a drug is listed in Tier III has nothing to do with its efficacy. (*Id.* at 410:25-411:4.) "Co-pay," of course, refers to the fixed sum of money an insurance company requires its insured to pay when having a prescription filled.

99. Par's internal forecasts for controlled release tramadol projected that its proposed generic would sell 2.5 million bottles and generate $68.5 million in revenue in the first three years on the market. (PTX-321 at PAR052811; Campanelli,[39] Tr. 457:17-458:24.) That forecast indicates significant potential for commercial success of controlled release tramadol products, including Ultram ER. Par's products are typically discounted by 70% to 90% of the price of the branded product. (Saber,[40] Tr. 757:3-18.) Thus, assuming inelastic demand, Par's three-year forecast suggests that a branded controlled release tramadol product could generate up to $685 million in that same time frame. That estimate reflects an increase over the sales of Ultram ER during the previous three years: from the time of its launch in February 2006 through the first quarter of 2009, sales of Ultram ER have generated approximately $500 million. (Axenroth, Tr. 411:14-20.)

100. It is undisputed that whatever commercial success Ultram ER has enjoyed so far and may enjoy in the future is related to the claimed features of the patents-in-suit. (Rausser, Tr. 811:19-24.)

H. *Par's Copying of Ultram ER*

101. Par began work on a generic copy of Ultram ER in 2006. (Mittleberg, Tr. 433:18-21.) From the start, Par assigned the product a very high priority. Par's Executive Vice President of Pharmaceutical Research and Development, Dr. Eric

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[39]Paul Campanelli is president of Par's generics division. (Campanelli, Tr. 455:19-24.)

[40]David A. Saber is the director of business development and licensing for Par's generics division. (Saber, Tr. 753:5-24.)

Mittleberg, could not recall at his deposition why Par selected tramadol as an active ingredient for a controlled release formulation.[41] (Mittleberg, Tr. 432:14-433:24.) Nonetheless, Par's Director of Regulatory Affairs, Ms. Kala Patel, recorded Mittleberg

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[41]Though not true of all of Par's employee witnesses, many were evasive and unconvincingly forgetful with respect to the process of developing their controlled release tramadol product. One particularly memorable example of Par's stonewalling is found in the following excerpt from the deposition of Par's senior scientist in charge of formulating Tramadol ER:

Q. [A]s senior scientist, ... what are the duties and responsibilities that you have?
A. I formulate.
Q. And what are the types of activities that are encompassed by when you say you formulate?
A. I don't know. I just formulate.
...
Q. How many different formulations did you make of Tramadol ER?
A. I don't remember.
Q. Was it more than 10?
A. I don't remember.
Q. Was it more than 20?
A. I don't remember.
Q. Was it more than 30?
A. I don't remember.
Q. Was it more than 50?
A. I don't remember.
Q. Was it more than a hundred?
A. I don't remember.
Q. Is it possible you made more than 100 different formulations of Tramadol ER?
A. I don't remember.
Q. Is there anything at all you remember about formulating Tramadol ER?
A. I formulated it.

(Shankar, Tr. 459:19-461:22.) This is only one example of several from different witnesses whose testimony is not discussed because it ultimately does not have a bearing on the disposition of the case. Suffice it to say, however, that, while Par obtains a favorable ruling on invalidity in this case, any success it has had here is in spite of and not because of the impression left by such obviously elusive tactics. Collective amnesia is an inappropriate and unimpressive litigation stance.

as saying that tramadol ER was a "[v]ery valuable FTF [First To File]" and that he wanted to pursue it with extreme aggressiveness. (Patel Tr. 443:5-444:9; PTX-246.) As mentioned, Par forecasted high sales for the first three years after launch. (FF ¶ 99.) The President of Par's generics division, Paul Campanelli, testified that if Tramadol ER were launched in 2009, it could be one of Par's top 20 products. (Campanelli, Tr. 455:7-21, 457:5-16.)

102. Par's strategy was to match the *in vitro* dissolution profile of Ultram ER (Mittleberg, Tr. 436:9-25; PTX-201 at PAR003502), and its dissolution tests showed it succeeded in doing that (Davies, Tr. 675:17-678:23; PTX-220 at PAR003756-57). Par's PK studies demonstrated that its formulation also matches the blood plasma curve of Ultram ER. (Davies Tr. 682:7-683:22; PTX-214 at PAR011462-66.)

103. Par's formulation is virtually identical to Ultram ER. (Davies, Tr. 665:2-4; PTX-166 at PAR015918.) Like Ultram ER, Par achieves controlled release through a normal release tablet core with a controlled release coating. (Davies Tr. 661:2-662:12; PTX-166 at PAR015917, 921.)

104. A Product Development Report, prepared in support of Par's ANDA, notes that Par relied on a "patent" in the development of its product, although the whereabouts of the file containing that patent are unknown. (PTX-171 at PAR002035; Shankar Tr. 466:1-469:8.) A project status presentation by Par's senior scientist shows that Par particularly studied the '887 patent. (Davies Tr. 665:19-666:6; PTX-375 at PAR024373.) The same presentation shows that Par studied the formulation ingredients and dissolution profile of Ultram ER in making its Tramadol ER tablets.

(Davies Tr. 665:11-18; PTX-375 at PAR024374-75.) Par's choice of controlled release coating included water insoluble ethylcellulose, which the patents-in-suit describe as "particularly" suitable for that use, and polyvinylpyrrolidone, as described in claim 5 of the '430 patent. (Uncontroverted Facts, D.I. 318 at ¶ III.B.(26); Davies Tr. 661:4-662:7; PTX-1 at 4:47-51; PTX-4 at 12:61-63; PTX-166 at PAR015917.)

105. Par seeks FDA approval of its tablets to manage "moderate to moderately severe chronic pain in adults who require around the clock treatment of their pain for an extended period of time" and for once-daily dosing, the same indications that the FDA has approved for Ultram ER. (Uncontroverted Facts, D.I. 326 at ¶ III.B.(12), (21); Weinberger, Tr. 877:2-18; PTX-747 at BVF00190805, 816, 829.)

I. *Prosecution History of the Patents-in-Suit - Chapter II*

106. The following discussion of the prosecution history of the patents-in-suit deals with facts that are most directly relevant to the inequitable conduct contentions in the case. The centerpiece of Par's inequitable conduct argument relates to foreign proceedings regarding a foreign counterpart to the '887 and '430 patents, namely, European Patent No. 624,366 ("EP '366"). (Uncontroverted Facts, D.I. 326 at ¶ III.H.(68); *see* D.I. 337 at 26-36.) EP '366 is entitled "Controlled release formulation containing tramadol."

107. Roger Milnes is head of the patent department of Mundipharma Research and was the in-house patent agent for Napp most substantively involved with the preparation and prosecution of the asserted patents during the 1990s. (Milnes, Tr. 334:15-335:18, 353:18-354:20.) As noted (*supra* note 35), Clifford Davidson is

Plaintiffs' U.S. patent prosecution counsel. Davidson had primary responsibility for the prosecution of the '452 and '887 patents and supervised prosecution of the '430 patent. (Davidson, Tr. 236:18-238:5.)

i. *The Malkowska I Declaration*

108. The PTO issued its first office action in the prosecution of the original application for the patents-in-suit, the application for the '452 patent (FF ¶ 66-67), on April 18, 1995 (the "'452 office action"). The examiner rejected the claims as anticipated and/or obvious in light of the Merck/Bondi reference. (FF ¶ 76; Davidson, Tr. 269:13-70:9; DTX-11A at PAR045841-43.)

109. In rejecting the claims, the examiner stated that Merck/Bondi "discloses controlled release compositions wherein the active ingredient may be tramadol." (DTX-11A at PAR045841.) Acknowledging that the reference did not disclose the recited dissolution rates found in some of the claims set forth in the application for the '452 patent, the examiner nonetheless believed that "the prior art compositions are taught to have controlled release properties and would be expected to inherently possess characteristics within the recited ranges." (*Id.*)

110. The Merck/Bondi reference was also found to be particularly relevant to the prosecution of EP '366, according to an August 1994 search report from the European Patent Office (the "EPO"). (PTX-603 at 17.)

111. In response to that EPO report but before the '452 office action, Napp carried out two sets of experiments based on one of the example formulations disclosed in Merck/Bondi. The results of Napp's efforts in that regard were

memorialized in the first of two relevant declarations from inventor Sandra Malkowska (the "Malkowska I Declaration").[42] (PTX 452). Adrian Brown, a senior formulation scientist at Napp, performed the experiments, designated as Batch numbers F523/86 and F523/106, under Prater's and Malkowska's supervision. (Prater, Tr. 109:2-112:9, 138:18-21; PTX-452; DTX-109.) The experiments used Example 1 of the Merck/Bondi reference, which describes a tablet with L-dopa as the active ingredient, coated by a solution of PVA at 1% to 5% of the total tablet weight, but the experiments substituted 200 mg of tramadol Hcl as the active ingredient. (PTX-452 at DDK 0006823; DTX-16 at NAPP0045472.) Tramadol Hcl is normally dosed at 100 to 400 mg. Napp chose to use Example 1 of Merck/Bondi because it uses 250 mg of L-dopa, which falls within that 100 to 400 mg dosing range for tramadol Hcl. (PTX-452 at DDK 0006823; DTX-16 at NAPP0045472.) Using 200 mg tramadol rather than 250 mg L-dopa as the active ingredient meant that the target tablet core weight for the tablets in Napp's experiments was to be 352 mg rather than the 402 mg weight disclosed in Example 1. (DTX-16 at NAPP0045472; PTX-452 at DDK0006823.)

112. Brown drafted two file notes dated December 8, 1994, and March 17, 1995, reporting his results. (DTX-109 at NAPP0037293-96; DTX-225.) Both notes state that the target tablet core weight for the experiment was 352 mg, but that the actual average tablet core weight was 340 mg (Prater, Tr. 161:21-162:1) and that the

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[42]I will refer to the two Malkowska Declarations by number according to their chronology, but neither of them are numbered on their face. (Tr. 321:3-322:7.) Although Malkowska submitted another declaration to the EPO (*id.*; PTX-614 at PUR1109643-44), that declaration is not relevant to this case and therefore is referenced only in passing. (*See infra* note 47.)

blend of ingredients during the experiments "exhibited poor flow characteristics." (DTX-109 at NAPP0037294; DTX-225 at NAPP 75930; Palmieri, Tr. 1365:16-1366:4.) "Flow characteristics" is a reference to the flow of powder ingredients within the tablet making machinery. According to Par's expert Dr. Palmieri, the "poor flow characteristics" that Brown reported were a result of using a gravity-fed tablet press. (Palmieri, Tr. 1364:11-1365:6.) Dr. Palmieri testified that it was known in the art that poor powder flow causes underweight tablets, because the powder does not properly flow into the die of the tablet press, and that the problem of poor flow could be remedied by switching from a gravity-fed tablet press to a force-fed tablet press. (*Id.* at 1366:5-1367:3.)

113. The dissolution results for Batch numbers F523/86 and F523/106 fell outside the scope of the asserted claims and were included in the Malkowska I Declaration. (Prater, Tr. 156:4-10; DTX-109 at NAP0037292; PTX-452 at DDK0006825.) There were, however, some notable irregularities with the declaration. First, some of the reported data showed that the percent of dissolved tramadol was above 100%. (PTX-452 at DDK 0006825.) Par asserts that such data would have suggested to a person with ordinary skill in the art that something was wrong with the experiment. (Palmieri, Tr. 1363:2-21.) Second, the Malkowska I Declaration omits the two noted difficulties Brown had in recreating Example 1 of Merck/Bondi. Specifically, the declaration incorrectly reported an average tablet core weight of 352 mg and failed to mention the "poor flow characteristics" Brown had observed during the mixing of the drug. (PTX-452 at DDK 0006823; Prater, Tr. 161:21-62:16, Malkowska, Tr. 1079:22-1080:3, 1090:25-1091:17.) Brown's internal file note contains the following statement:

"Tablets were compressed using 3/8" round shallow concave, bevelled edge tooling on a Kilian rotary tablet machine to an average tablet weight of *340 mg* and 6 kp hardness. *The blend exhibited poor flow characteristics*." (DTX-109 at NAPP0037294 (emphasis added).) The Malkowska I Declaration included the exact same statement, but with the tablet weight as 352 mg and the "poor flow" comment deleted. (PTX-452 at DDK 0006823.) Third, the Malkowska I Declaration used data from only one tablet, the one that fell the furthest outside the claimed dissolution ranges, rather than an average of all the tested tablets. (Palmieri, Tr. 1377:24-1378:20.) Prater testified that the reference to the dissolution rate of a single tablet was an "oversight." (Prater, Tr. 1456:20-1458:6.)

114. Milnes prepared and submitted the Malkowska I Declaration to the EPO as a part of the prosecution of EP '366. (PTX-452; Milnes, Tr. 344:24-346:12.) Davidson also relied on the Malkowska I Declaration, including it in a response to the '452 office action and arguing to the PTO that the Merck/Bondi reference was not enabling. (Davidson, Tr. 270:10-72:24; DTX-11B at PAR045887-88.) Whether Davidson was aware of the differences between the Malkowska I Declaration and Brown's file notes is unclear.

115. As a part of its inequitable conduct argument, Par criticizes the Merck/Bondi experiments on which the Malkowska I Declaration was based. (D.I. 339 at ¶¶ 101-03.) At trial, Dr. Palmieri testified that the experiments were flawed because one of ordinary skill in the art would not have conducted dissolution testing on the tablets since they were underweight. (Palmieri, Tr. 1364:11-1365:6.) Par also relies on

the three irregularities with the Malkowska I Declaration discussed above, i.e., the reporting of dissolutions above 100%, the discrepancies between the declaration and Brown's notes, and the reporting of only one tablet's dissolution rate rather than an average rate. (D.I. 339 at ¶¶ 99, 104-06.)

116. As discussed below (CL, *infra*, ¶ 70), I conclude that the omissions and misrepresentations in the Malkowska I Declaration, while disturbing, are not clearly and convincingly material.

117. Both the EP '366 patent and the '452 patent were granted following the submission of the Malkowska I Declaration.

ii. *World Congress of Pain*

118. In 1996, representatives of Grünenthal and Mundipharma met twice to discuss the companies' patent positions with respect to controlled release tramadol. (DTX-166; DTX-167.) At the second meeting, Grünenthal disclosed to Mundipharma that it had conducted clinical studies with an extended release tramadol formulation before the filing date of the German priority document and that the results of those studies were presented at the Seventh World Congress on Pain in August of 1993 ("World Congress of Pain Abstracts"). (DTX-167 at NAPP0394555.) The existence and content of those discussions and the World Congress of Pain Abstracts were never disclosed to the PTO.

iii. *EP '366 Opposition Proceedings and the Malkowska II Declaration*

119. EP '366 subsequently underwent opposition proceedings. (Milnes, Tr. 346:22-47:13.) Parties in the proceedings criticized the Malkowska I Declaration for

reporting dissolution for tramadol going beyond 100%. (PTX-459 at DDK 7346; PTX-489 at NAPP0078520_002.)

120. In response, and while the prosecution of the '887 patent was ongoing, Napp normalized the data of the Malkowska I Declaration, so that the maximum dissolution value was 100%. (DTX-247 at NAPP41839.) The normalized data was closer to the claimed ranges than the results disclosed in the Malkowska I Declaration, but still fell outside of them. Plaintiffs did not disclose the normalized data to the European or U.S. Patent Offices.

121. To better confirm that Merck/Bondi did not inherently disclose the claimed dissolution rates, Napp repeated the experiments underlying the Malkowska I Declaration. (Milnes, Tr. 347:14-349:12; PTX-489 at NAPP0078520_002.) An email from Brown, who was again instructed to carry out the experiments, reveals that he did not want to write up experiments that produced "a documented and unacceptable profile." (DTX-260; *see* Prater, Tr. 118:5-22.)

122. Brown ran the initial coating run at a coating spray rate of 3 g/min, as was done in the 1995 experiments. (PTX-436 at NAPP373632.) That coating run, labeled Batch 616/07, failed "due to over wetting and sticking."[43] (PTX-437 at NAPP406447; Palmieri, Tr. 1386:7-22.)

123. Although dissolution tests were conducted on Batch 616/07, Par does not argue that the results of those tests should have been submitted to the PTO. (DTX-253

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[43]"Sticking" refers to the adherence of the drug substance to manufacturing equipment, such as the punch faces of a tablet-making press. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1354 (Fed. Cir. 2007).

at NAPP0041855; D.I. 340[44] at 26, 28.) Instead, Par argues that the sticking encountered with Batch 616/07 reflects problems arising out of the use of a 3 g/min spray rate, the same spray rate that was used for the experiments that formed the basis of the Malkowska I Declaration. (D.I. 340 at 29; D.I. 339 at ¶ 118.) Plaintiffs counter that the sticking was due to conditions unrelated to the Malkowska I Declaration, namely the low inlet and outlet temperatures in the coater. (D.I. 334 at ¶ 146.)

124. I find Plaintiffs' explanation credible. The notes Brown made during coating of tablets for which sticking was a problem reveal that the inlet and outlet temperatures were lower than the target temperatures for the batch. Once the temperatures reached the target level, no sticking occurred even at the 3 g/min spray rate. (PTX-436A at NAPP0373633 [F616/11].)

125. Because of the sticking problem, a second coating run was conducted. (PTX-436 at NAPP373632.) For the second coating run, labeled F616/07B, a slower spray rate of 2 g/min was used, and Brown reported that "the slower spray rate of 2 g/min resulted in a smoother coat." (DTX-252 at NAPP 78521_004.) No sticking comments were reported in the laboratory notebooks for F616/07B. (DTX-252 at NAPP 78521_007; Malkowska, Tr. 1125:25-26:9.)

126. Dissolution tests were performed on the F616/07B batch and identified as LIMS Sample ID code 97000506.[45] (Prater, Tr. 165:11-23; DTX-251; DTX-254,

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[44]D.I. 340 is Par's post-trial brief.

[45]"LIMS" means Laboratory Information Management System. (Prater, Tr. 164:24-165:5.) A LIMS number is a unique number used by Napp to identify particular analytical tests. (*Id.* at 165:7-10.)

Malkowska, Tr. 1128:9-22.) When Brown obtained the dissolution report for LIMS Sample 97000506 on September 26, 1997, he forwarded the results to Malkowska with the handwritten notation: "These are the TMDOL/PVA coated tablets corrected for assay." (DTX-251; Malkowska, Tr. 1112:25-13:6.)

127. The average tablet dissolution data from the F616/07B batch minus the standard deviation was within a half percentage point of the claimed dissolution range. (Palmieri, Tr. 1377:19-78:20, 1405:11-1408:13.) The data and results from batch F616/07B were never disclosed to the European or U.S. Patent Offices. (Prater, Tr. 167:13-25.)

128. Malkowska knew about the dissolution results of Batch F616/07B and may have recognized their full import. She asked Brown to find and photocopy the results, and then asked him, "compared with original data is coating same? Need this urgently this afternoon." (DTX-249 at NAPP 41852; Malkowska, Tr. 1105:1-17.) Brown responded to Malkowska's question by forwarding a copy of the LIMS report for Sample 97000506 with the handwritten note: "Second coating run, corrected for assay. Same coating, but slower spray rate used which may have (slightly) improved the smoothness of the coat." (DTX-249 at NAPP 41853.) Prater, as Brown's direct supervisor, likely knew about the testing results as well. (Malkowska, Tr. 1138:4-8.) Milnes, however, apparently was not made aware of the results. (*Id.* at 1137:11-11-23.)

129. About two weeks later, Brown went back into the laboratory to do a new coating run, Batch F616/14, as recorded in an entry dated October 24, 1997. (PTX-436 at NAPP 373635.) Brown wrote that "the coating run needs to be repeated using the same coating conditions used for F423/08 and F616/08," which included the coating

spray rate of 3 g/min. (PTX-436 at 373635; Palmieri, Tr. 1386:7-22; Malkowska, Tr. 1120:8-1121:24.) There were no comments about sticking in the batch record for F616/14. (Prater, Tr. 149:2-9, 1467:15-68:8; PTX-436A at NAPP0373635.)

130. The dissolution rates of batch F616/14 were tested and fell outside of the claimed ranges. (Prater Tr. 147:4-12,156:11-14; Milnes Tr. 347:14-348:22; PTX-489 at NAPP0078520; PTX-459 at DDK0007346.) The results were included in another Malkowska Declaration (the "Malkowska II Declaration"), which stated that tramadol preparations made according to Merck/Bondi have release rates "significantly faster than" the EP '366 claims and "demonstrate no real control of the release of tramadol." (PTX-459 at DDK 7346.) As with the Malkowska I Declaration, Milnes drafted the Malkowska II Declaration. (Milnes, Tr. 349:15-350:1.) Malkowska was asked at her videotaped deposition, which was played at trial, why the dissolution results of Batch F616/07B were not included in her declaration. (Tr. 1111:18-20.) She responded that she did not know why, and that response appeared to be genuine. (*Id.* at 1111:18-1112:24).

131. The Malkowska II Declaration was submitted to the EPO as a part of the opposition proceedings, and the EPO issued a preliminary opinion that EP '366 was valid over the prior art.[46] (PTX-623 at PUR1110054-56; Milnes, Tr. 347:14-17.) Davidson subsequently submitted the Malkowska II Declaration to the PTO during

[46]EP '366 was ultimately revoked because an amendment made during prosecution was not of an allowable form. (Milnes, Tr. 350:2-51:18.)

prosecution of the '887 and '430 patents. (PTX-459; PTX-614 at PUR1109644; PTX-623 at PUR1110071.[47])

iv. *Napp Repeat Experiments*

132. In 1998, Napp filed an action against Asta Medica Limited ("Asta") in the United Kingdom alleging infringement of EP '366 ("the U.K. Litigation"). (Uncontroverted Facts, D.I. 326 at ¶ III.H.(73).)

133. In that suit, Napp submitted a report from Dr. Alexander Florence (PTX-473) and, later, a supplemental report ("Florence supplemental report") (PTX-472). (Uncontroverted Facts, D.I. 318 at ¶ III.H.(75).) Asta submitted its own expert report from Dr. John Tasker Fell (PTX-455) and a supplemental report as well ("Fell supplemental report") (PTX-474). (Uncontroverted Facts, D.I. 318 at ¶ III.H.(76).)

134. As a part of the U.K. Litigation, Napp again set out to repeat experiments regarding Merck/Bondi (the "Napp repeat experiments"). (DTX-160.) On November 3, 1998, Napp's U.K. Litigation counsel, Lovell, White & Durant ("LWD"), sent to Davidson and Milnes, among others, an "URGENT" facsimile, which forwarded Napp's Notice of Experiment to be served later that day. (DTX-160; Davidson, Tr. 276:5-277:13.) The Notice indicated that experiments were going to be conducted following Merck/Bondi that were designed to produce the same results as the Malkowska II Declaration. (Davidson, Tr. 277:2-279:13; DTX-160 at DDK15068, 15078-80; Prater, Tr. 125:5-17; DTX-259.) Napp employees, supervised by Prater, conducted the Napp repeat experiments in the presence of experts and lawyers from both Napp and Asta from

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[47]PTX-614 and -623 refer to the Malkowska II Declaration as the "third Malkowska Declaration." (*See supra* note 42.)

December 15 to December 22, 1998. (Prater, Tr. 123:20-124:11; DTX-236; PTX-472 at ¶ 8; PTX-474 at ¶ 11.) Paul Cowcher, a supervisor of laboratory analysis at Napp, performed the analytical work. (Cowcher, Tr. 1173:4-11, 1180:6-11; DTX-235; DTX-259.) Brown again did the formulation work. (Cowcher, Tr. 1180:13-16; DTX-234; DTX-259; Prater, Tr. 126:12-127:15.)

135. On the first day of the experiments, Brown indicated that attempts to make tablets using the Kilian gravity-fed press, the same type of press that was used in the experiments underlying the Malkowska Declarations, resulted in problems with die fill and tablet weight, so they switched to a force-fed press. No problems were encountered after the switch. (DTX-234; Palmieri, Tr. 128:2-130:14.)

136. The dissolution profile of the tested batch, F644/32D, fell within the claimed ranges. (Prater, Tr. 156:15-18.) These results were reported in the Florence and Fell supplemental reports to the court presiding over the U.K. Litigation. (PTX-472 at ¶ 8; PTX-474 at ¶ 12.) Both sides' experts in the U.K. Litigation agreed that the repeat experiments gave results that contradicted the Malkowska Declarations. (PTX-472 at ¶ 8; PTX-474 at ¶ 12.) On December 23, 1998, LWD sent a letter to Napp, copying Davidson and Milnes, that stated, "[I]t is necessary that we have a precise understanding of the reasons for the failure of these experiments" and requested a report by January 5, 1999.[48] (DTX-512; Davidson, Tr. 280:13-283:8.) A reasonable

[48]The use of the term "failure" may be seen as a comment on Napp's mindset, i.e., that the goal of the Napp repeat experiments was to confirm the conclusions found in the Malkowska Declarations. Since the results had the opposite effect, the experiments were, given that goal, a failure.

patent examiner would have found the results of the Napp repeat experiments relevant to determining whether to allow the claims of the patents-in-suit.

137. On January 8, 1999, Dr. Margaret Dyer, the section manager of the formulation department at Mundipharma Research, reported to Prater that the tablets in F644/32D had a 6.6% PVA coating instead of the 5% coating described in Example 1 and claim 2 of the Merck/Bondi reference. (Prater, Tr. 111:15-20, 156:19-158:20; DTX-236 at NAPP0078491_003-004.)

138. In addition to the Napp repeat experiments, experiments based on the Merck/Bondi reference were conducted as a part of the opposition proceedings against EP '366, the foreign counterpart to the patents-in-suit. (*See* FF ¶ 106.) The results of those experiments were included in the "Posch report," dated February 25, 1999. (PTX-461) Likewise, Asta did experiments, the results of which were included in the "Momberger report," dated July 15, 1998, and the "Report of Repeat Experiment," dated November 26, 1998. (PTX-450; PTX-451.) These reports were consistent with the results in the Malkowska Declarations that tablets coated with 5% or less PVA, in accordance with Merck/Bondi Example 1 and claim 2, fell outside of the claimed dissolution ranges. (Palmieri, Tr. 1413:10-1414:4; PTX-450 at DDK0007216; PTX-451 at DDK0006806; PTX-461 at DDK0007394.) Those reports also showed that different results falling within the claimed ranges could be obtained by deviating from Merck/Bondi Example 1, such as by using a thicker PVA coat. (*See* PTX-614 at PUR1109645.)

139. On March 21, 1999, Asta and Napp executed an agreement settling the U.K. Litigation. (DTX-30.) Pursuant to the Settlement Agreement, Asta obtained a royalty-free license in all countries other than the United States and Canada. (DTX-30 at DDK 13903; 13907-10.)

140. Davidson was included in the discussion of the Napp repeat experiments and knew about the results of those experiments when Napp obtained them in December of 1998, or shortly thereafter. (DTX-160; DTX-512; Davidson, Tr. 275:3-277:21; DTX-162 at DDK013872-875; DTX-976 at 74-75, 80, 82, 157-64, 167-69.) Because he generally received and reviewed documents from the U.K. Litigation in order to determine whether they should be brought to the attention of the PTO, it is very likely that Davidson also received the Florence and Fell supplemental reports shortly after they were submitted to the court in the U.K. Litigation. (Davidson, Tr. 277:14-21.) The copy of the Florence supplemental report in the record here is undated but was in all likelihood finalized before the U.K. Litigation was settled on March 22, 1999. (DTX-30.) The Fell supplemental report is dated March 8, 1999. (PTX-474 at DDK 0007023.)

141. Davidson submitted the Florence and Fell supplemental reports to the PTO, as well as the Posch report, in an information disclosure statement ("IDS") dated March 10, 2000, during prosecution of the '887 patent. (PTX-614; PTX-2 at PUR1109645, 47-48.) A year before that, on March 1, 1999, contemporaneously with the drafting of the Florence and Fell supplemental reports in the U.K. Litigation, Davidson submitted an IDS to the PTO discussing Asta's arguments in the U.K.

Litigation. (PTX-611 at PUR1109610.) Davidson contended that, although Asta argued that experiments based on Merck/Bondi showed that the reference reads on EP '366, "the evidence is to the contrary." (*Id.*) Davidson's March 1, 1999 IDS included the Momberger Report and the Report of Repeat Experiment but did not mention the results of the Napp repeat experiments. (*Id.* at PUR1109610-12; Davidson, Tr. 300:15-301:12.) Davidson continued to rely on the Malkowska I Declaration in the March 1999 IDS. (PTX-611 at PUR1109612.)

142. Also on March 1, 1999, Davidson submitted a response to an earlier office action issued by the PTO. (PTX-863.) In that earlier office action, the examiner reported that the application for the '887 patent was in condition for allowance except for "formal matters." (DTX-5A at PAR046253.) Accordingly, the examiner closed prosecution on the merits, but, in response to an earlier IDS that disclosed 129 references raised in the EP '366 opposition proceedings, requested that the applicants submit a brief summary of each of the references and their relevance to the pending claims. (*Id.* at PAR046254.) The examiner warned the applicants that "an applicant may be guilty of inequitable conduct if the applicant is aware that certain references within a large information disclosure statement are more material tha[n] the rest and does not inform the PTO as to which references the applicant considers to be most material." (DTX-5A at PAR46254 (citations omitted).) In his March 1999 response, Davidson "acknowledged and appreciated" the examiner's concern and provided summaries of every reference cited and positions taken by the opponents as to their pertinence. (PTX-863 at PUR1109569-70; PTX-864.) Davidson indicated, however,

that the applicants could not choose between the opponents' various positions on the pertinence of the art and urged the examiner to review the underlying documents "separate and apart" from the summaries. (*Id.* at 1109570-71.) To give the examiner further opportunity to review the submitted documents, Davidson paid an additional fee and filed a continued prosecution application, which had the effect of reopening prosecution on the merits. (Davidson, Tr. 247:2-249:17; PTX-863 at PUR1109581.)

143. In the March 2000 IDS disclosing the Florence and Fell supplemental reports, the first six pages of the March 1999 IDS relating to the U.K. Litigation are repeated almost verbatim. (PTX-611; Davidson, Tr. 329:21-333:8.) The first eight exhibits to the March 2000 IDS were identical to those submitted with the March 1999 IDS. (Davidson, Tr. 317:25-318:9.) On page 10 of the March 2000 IDS, the first page of new material relating to the U.K. Litigation, Davidson referenced the Florence supplemental report and attached the report as Exhibit "W," near the middle of the submission. (PTX-614 at PUR1109647; Davidson, Tr. 332:2-9.) Davidson stated that the Florence supplemental report noted that the tabletting machine had changed as compared to the machine in the original experiment. (PTX-614 at PUR1109647 n.3.) Davidson did not highlight, however, that Professor Florence stated in his supplemental report that the machine was changed because "the apparent quality of the tablets produced using the original machine was not good enough." (PTX-472 at ¶ 8.)

144. Following the March 2000 IDS, the examiner issued the June 2000 office action (FF ¶¶ 75, 77), in which he maintained a rejection based on the Merck/Bondi reference and invited the applicants to schedule a personal interview to discuss the references pertaining to the U.K. Litigation. (PTX-2 at 1109661-64.) Davidson

accepted that invitation. (Davidson, Tr. 258:15-259:12.) The experimental evidence with respect to the EP '366 opposition proceedings and the U.K. Litigation was discussed during the interview, but, according to Davidson's subsequent submission to the PTO, the examiner did not rely upon that discussion "as a basis for removing the previous rejection on the merits." (PTX-2 at PUR1109672.)

145. Davidson also submitted a copy of the March 2000 IDS to the PTO during prosecution of the '430 patent. (PTX-5 at PUR1110009, PUR1110061.) Even though some of the reports submitted as a part of that IDS arguably revealed that by following Example 1 of the Merck/Bondi reference one can formulate a tablet with dissolution rates that fall within the claimed ranges, Davidson continued to affirmatively rely on the Malkowska I Declaration in support of patentability. (*Id.* at PUR1110113-14.)

III. CONCLUSIONS OF LAW

1. Jurisdiction over the subject matter of this action is proper under 28 U.S.C. §§ 1331 and 1338(a).

A. *Infringement*

2. Patent infringement is making, using, importing, offering to sell, or selling a patented invention without authority. 35 U.S.C. § 271(a). Under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355; 35 U.S.C. §§ 156, 271, 282), it is an act of infringement to submit an ANDA for a drug claimed in a patent. 35 U.S.C. § 271(e)(2)(A).

3. An infringement analysis entails two steps. The first step is determining the meaning and scope of the patent claims asserted to be infringed, and the second step is comparing the properly construed claims to the accused product. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996).

4. The first step, claim construction, is designated a pure issue of law. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1455-56 (Fed. Cir. 1998) (en banc). *But see id.* at 1478 (Rader, J., dissenting in part) ("[C]laim construction requires assessment of custom and usage in the relevant art, assessment of events during prosecution, assessment of the level of ordinary skill in the art, assessment of the understanding of skilled artisans at the time of invention–to name just a few factual

components of the complex process of claim interpretation."). Previously, I construed a number of claim terms as follows:

- "therapeutic effect" means "an effective treatment for pain";
- "A [solid] controlled release oral [dosage form/pharmaceutical preparation/pharmaceutical tablet] ... said [dosage form/pharmaceutical preparation/pharmaceutical tablet] providing a therapeutic effect for [at least] about 24 hours" means "a single tablet, not including additional or previously administered tablets, that provides a therapeutic effect for [at least] about 24 hours";
- "therapeutic effect for about 24 hours after oral administration" means "an effective treatment of pain for about 24 hours from when the treatment begins to provide its intended effect";
- "therapeutic effect for at least about 24 hours" means "an effective treatment for pain for about 24 hours, or longer, from when the treatment begins to provide its intended effect";
- "a pharmaceutically effective amount of tramadol or a salt thereof" means "an amount of tramadol or its salt sufficient to achieve a therapeutic effect";
- "matrix" means "pharmaceutical preparation that incorporates the active ingredient dispersed within a solid dosage form"; and
- "normal release matrix" means "a matrix that releases the active ingredient as quickly as feasible."

Claim Construction Opinion, 584 F. Supp. 2d at 680.

5. As to the second step of the infringement analysis, Plaintiffs bear the burden of proving that the accused product meets each and every limitation of the construed claims by a preponderance of the evidence. *Catalina Lighting, Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1285 (Fed. Cir. 2002). Where the act of infringement is the filing of an ANDA, the analysis is a hypothetical one, comparing the asserted claims against the product that is likely to be sold should the FDA approve the application.

Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1248-49 (Fed. Cir. 2000). "This hypothetical inquiry is properly grounded in the ANDA application and the extensive materials typically submitted in its support." *Id.* at 1248 (quotation omitted).[49] Therefore, it is proper for me to consider the ANDA itself, materials submitted by the ANDA applicant in support of its ANDA, and any other pertinent evidence. *Id.* at 1248-49; *Glaxo, Inc.*, 110 F.3d at 1570.

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[49]The *Bayer* analysis is applicable to Plaintiffs' claims of infringement of the '430 patent as well as the '887 patent. The '430 patent was issued following the FDA's approval of Ultram ER, and, unlike the '887 patent, is not listed in the Orange Book. *See* 21 U.S.C. § 355(b)(1) (requiring an NDA applicant to disclose to the FDA only those patents issued as of the date of the filing of the NDA or those issuing during the pendency of the NDA). But there is no requirement that infringement actions against ANDA filers must be based on patents listed in the Orange Book. *See Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1343-44 (Fed. Cir. 2004) (adjudicating patent infringement case triggered by ANDA filing even though patents-in-suit were not listed in Orange Book); 35 U.S.C. § 271(e)(2)(A) (making it an act of infringement to submit an ANDA "for a drug claimed in a patent").

For that reason, Plaintiffs may have been able to make § 271(e)(2)(A) the basis for their claim of infringement of the '430 patent. *See Glaxo Group*, 376 F.3d at 1344 (holding that, even though patents-in-suit were not listed in Orange Book, "[s]ection 271(e)(2)(A) provides a jurisdictional basis for a declaratory judgment suit against a generic manufacturer"); *see also Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997) ("[Section] 271(e)(2) provided patentees with a defined act of infringement sufficient to create case or controversy jurisdiction to enable a court to promptly resolve any dispute concerning infringement and validity."). Instead, Plaintiffs allege only that, "once the FDA grants tentative approval of Par's ANDA, Par will undertake substantial activities directed toward engaging in infringement ... of the ['430 patent by making, using and undertaking substantial preparations for offering to sell, without authority from plaintiffs, its Tablets." (D.I. 78 at 5-6.) How far an ANDA filing will go in permitting a branded drug manufacturer to bring a declaratory judgment action based on such an allegation is unclear. *See Glaxo, Inc.*, 110 F.3d at 1568 ("While performing development work and seeking [ANDA] approval, a generic drug manufacturer is free from liability for patent infringement based solely upon acts necessary to prepare the ANDA.") (citing 35 U.S.C. § 271(e)(1)). But in this case the '430 patent is sufficiently related, as a continuation of the patent used for the § 271(e)(2)(A) claim, to put it in play. In any event, the parties do not dispute that there is an adequate basis for declaratory judgment jurisdiction here, and I agree that there is.

6. I conclude that Par's tablets will literally infringe claims 3, 13, 27, and 29 of the '887 patent and claims 5, 7, and 11 of the '430 patent.

i. *'887 Patent*

7. Claim 1 of the '887 patent, from which both claims 3 and 27 depend, and claim 13, from which claim 29 depends, require that the claimed oral pharmaceutical preparation (or oral pharmaceutical tablet) provide a therapeutic effect for approximately 24. (FF ¶ 40.) The parties focus their dispute on whether that limitation has been met. As set out above (FF ¶ 44), Plaintiffs attempt to show that Par's tablets have a 24 hour therapeutic effect by comparing the PK data of Ultram ER and Ultram IR.

8. I have already concluded that the efficacy of Ultram IR is a proper basis for measuring the efficacy of Ultram ER (FF ¶ 60) and that a 50 mg dose of Ultram IR has an onset of action at about 30 minutes (FF ¶ 52). Dr. Davies opined for Plaintiffs that, because the onset concentration of 50 mg of Ultram IR is 40 ng/ml, one should look to how long a 200 mg Ultram ER dose remains above that 40 ng/ml threshold to determine the duration of the therapeutic effect. (*See* FF ¶ 61.)

9. Par responds that Dr. Davies is effectively establishing an MEC for tramadol (*see* FF ¶ 22), which, Par argues, is contradicted by Dr. Grond's testimony, not to mention Plaintiffs' own concession that an MEC for tramadol has not been established. (Grond, Tr. 987:3-987:21; D.I. 331 at 15.) But accepting that an MEC for tramadol has never been established in scientific studies of the sort Par would acknowledge does not doom Plaintiffs' argument. To the extent that one uses Ultram

IR as a marker for efficacy — an approach that the FDA has sanctioned (FF ¶ 59) and that the Napp scientists used while developing the patents-in-suit (FF ¶ 27) — the evidence supports a finding that there is some efficacy at 40 ng/ml.

10. Par also responds to Plaintiffs' infringement argument by pointing to Dr. Grond's testimony that a 40 ng/ml plasma concentration is "much, much, much lower than any value I've ever seen from somebody who has discussed []minimum effective concentration" of tramadol. (Tr. 1004:1-6.) Dr. Grond highlighted studies that evaluated the effectiveness of intravenous injections of tramadol and that suggested various higher MEC values ranging from 960 ng/ml (Grond, Tr. 991:25-992:5) to 287.7 ng/ml (DTX-95 at NAPP0183181; Grond, Tr. 992:5-7).[50] Par thereby argues that even if one could compare Ultram IR to Ultram ER to establish efficacy, a 40 ng/ml level is simply too low a value to use to conduct that comparison. To emphasize the point, Par highlights that even a single dose of 100 mg Ultram IR appears to maintain a blood plasma concentration above 40 ng/ml for about 24 hours. Thus, according to Par, adopting Plaintiffs' approach has the anomalistic result of demonstrating that a single 100 mg Ultram IR tablet provides a therapeutic effect for about 24 hours, even though the immediate release pill is not normally prescribed with that effect in mind. (Davies, Tr. 739:25-743:10, 746:21-747:3.)

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[50]The paper discussing the study that suggested a 960 ng/ml MEC, Hackl (1986), is not in the record. Nonetheless, the later paper suggesting a 287.7 ng/ml MEC, Lehmann (1990), discusses the Hackl reference and notes that, because the studies were similar, the reasons for the discrepancy in MEC are unclear. (DTX-95 at NAPP0183181.)

11. Par's critique has some force. Ultimately, however, I am unpersuaded. To the extent that there are studies suggesting a higher MEC, Dr. Grond acknowledges that they are inconclusive. (Grond, Tr. 991:15-993:3.) But more importantly, that studies have suggested a higher MEC of intravenously administered tramadol is not directly relevant to determining at what blood plasma level a 50 mg Ultram IR tablet provides some pain relief. In construing the claims, I have already rejected Par's argument that Plaintiffs could only show that the accused tablets had a therapeutic effect through a clinical study that included controls to account for the placebo effect, noting that the patent itself relied on the generally acknowledged therapeutic effect of tramadol. *Claim Construction Opinion*, 584 F. Supp. 2d at 670-71. Similarly, that studies evaluating the therapeutic effect of Ultram IR fail to account for the placebo effect, and perhaps for that reason result in an onset concentration that is lower than any published MEC for tramadol standing alone, does not invalidate Plaintiffs' reliance on that onset concentration as a marker for therapeutic effect. Plaintiffs' burden is basically to establish that an "oral pharmaceutical preparation" containing tramadol provides a 24-hour therapeutic effect (*see* '887 patent, claim 1 12:32-34; '430 patent, claim 1 12:50-51), not that the tramadol in the preparation is the sole source of that 24-hour effect. The blood plasma level of tramadol at 30 minutes — the time that a 50 mg dose of Ultram IR is effective — although not an exact measure of the pain relief provided by tramadol, is an adequate proxy for measuring whether and for how long a single dose of a controlled release preparation containing tramadol will provide some therapeutic effect. The 100 mg, 200 mg, and 300 mg doses of Ultram ER provide

blood plasma levels above 40 ng/ml for at least 24 hours (*see* FF ¶¶ 61-63), and, as noted, given the evidence showing that the onset of action from Ultram IR begins at a point roughly coinciding with a blood plasma concentration of 40 ng/ml, I am persuaded that some therapeutic effect from Ultram ER will remain for as long as the concentration remains above that level.

12. I am also persuaded that Par's tablets will meet the 24-hour therapeutic effect limitation for one final reason. The "therapeutic effect" limitation generally speaks to whether the product works. That a sophisticated pharmaceutical company like Par would aggressively seek to introduce a generic version of a product, and forecast revenues exceeding $65 million over the first three years after launch (FF ¶¶ 99, 101), demonstrates Par's high confidence that the branded product indeed works. Par's business actions are more indicative of Ultram ER's efficacy than the litigation driven assertion that the therapeutic effect claimed in the patents-in-suit — the only limitation that Par argues is lacking in its proposed tablets — is illusory.[51]

13. The presence of the rest of the limitations in the asserted claims is easily established. Claim 1 of the '887 patent also requires a "controlled release oral pharmaceutical preparation suitable for dosing every 24 hours." ('887 patent,

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[51]Par has at times tried to draw a distinction between steady state and single dose efficacy. (*See* D.I. 340 at 3-4.) In theory, one could acknowledge the efficacy of Ultram ER at steady state without acknowledging that a 24-hour therapeutic effect is provided by, as I have construed the limitation, a single dose. But it is hard for me to believe, as a factfinder looking at the totality of the evidence presented here, that a product would have a market sufficient to warrant the entry of a generic competitor if it regularly took more than a day to adequately relieve moderate to moderately severe chronic pain. That is especially true where, as here, the market is already crowded with drugs that, one may reasonably believe, would provide much quicker pain relief. (*See* Axenroth Tr. 400:15-404:16; PTX-1093.)

12:16-17.) Par's product is a pharmaceutical preparation intended for oral administration that provides a controlled release of the drug and is intended to be administered once a day. (Uncontroverted Facts, D.I. 326 at ¶ III.B.(19)-(21); Davies, Tr. 661:10-662:12, 714:9-13.) Claim 1 also requires "a substrate comprising a pharmaceutically effective amount of tramadol or a salt thereof." ('887 patent, 12:18-19). The parties stipulated that the term "substrate" in the '887 patent means "[a] solid pharmaceutical preparation that contains the active ingredient." (D.I. 247 at 10). Par's product is a solid preparation containing tramadol Hcl, a salt of tramadol, in a pharmaceutically effective amount. (Uncontroverted Facts, D.I. 326 at ¶ III.B.(11), (22)-(24); Davies, Tr. 715:5-18.) Claim 1 further requires that the substrate be "coated with a controlled release coating." ('887 patent, 12:20). Par's product has a controlled release coating. (Davies, Tr. 661:10-662:7; PTX-166 at PAR015917, 921.)

14. Claim 3 of the '887 patent requires a specific *in vitro* dissolution profile "measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37ºC and using UV detection at 270 [n]m." ('887 patent, 12:51-53.) The claimed dissolution ranges are between 0% and 50% tramadol released after 1 hour, between 0% and 75% tramadol released after 2 hours, between 10% and 95% tramadol released after 4 hours, between 35% and 100% tramadol released after 8 hours, between 55% and 100% tramadol released after 12 hours, between 70% and 100% tramadol released after 16 hours, and greater than 90% tramadol released after 24 hours. (*Id.* at 12:50-65.)

15. Plaintiffs' expert, Dr. Fanfarillo, performed dissolution tests on all strengths of Par's tablets at the claimed conditions, using the "paddle method" described in the European Pharmacopeia. Dr. Fanfarillo's dissolution tests show that Par's tablets dissolve within the claimed dissolution ranges of all the asserted claims. (Fanfarillo,[52] Tr. 637:3-646:23; Davies, Tr. 667:8-672:21, 678:24-680:15:; PTX-533A, -533C.)

16. Internal testing by Par on its tablets prior to its ANDA filing confirms Dr. Fanfarillo's results. Although Par's tests were performed using the paddle method set forth in the U.S. Pharmacopeia, rather than the European Pharmacopeia, both parties' experts agree that the differences between these two methods are inconsequential. (Palmieri, Tr. 1329:10-24; Davies, Tr. 675:17-678:23; PTX-220 at PAR003756-57; PTX-365 at PAR021250).

17. Claim 13 of the '887 patent is similar to claim 1 except that claim 13 requires a "pharmaceutical tablet" instead of a "pharmaceutical preparation" and a "tablet" instead of a "substrate." ('887 patent, 13:53-14:16.) Par's product is a tablet. (Uncontroverted Facts, D.I. 326 at ¶ III.B.(7).)

18. Claim 13 and independent claim 1 of the '887 patent have broader dissolution ranges than claim 3 and add a dissolution range at 36 hours. ('887 patent, 13:62-14:3.) Because the dissolution profile of Par's tablets falls within the claim 3 ranges and provides greater than 80% tramadol released after 36 hours, it also falls within the claim 13 and claim 1 ranges. (Davies, Tr. 666:12-667:10; PTX-533A.)

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[52]Dr. Michael Fanfarillo is Operations Director for Molecular Profiles, a company that tests drug substances and drug products. (Fanfarillo, Tr. 633:9-634:1.)

19. Claim 13 also requires a W_{50} value (*see* FF ¶ 22) "in the range of 10 to 33 hours." ('887 patent, 14:3-4.) All strengths of Par's tablets have a W_{50} that is around 15 hours and therefore meet that element. (Davies, Tr. 715:19-717:8; PTX-214 at PAR011463.)

20. Claims 27 and 29 of the '887 patent depend respectively from claims 1 and 13 and further require that the controlled release coating "comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing." ('887 patent, 16:1-5, 12-16.) The controlled release coating on Par's tablet contains ethylcellulose, which is a water insoluble cellulose. (Uncontroverted Facts, D.I. 318 at ¶ III.B.(25)-(26); Davies Tr. 661:10-20; PTX-166 at PAR015917.)

ii. *'430 Patent*

21. The asserted claims in the '430 patent all depend from claim 1. ('430 patent, 12:54-57, 12:61-63, 13:1-12, 14:11-12.) Similar to the asserted claims in the '887 patent, claim 1 requires that the claimed solid controlled release oral dosage form provide a therapeutic effect for approximately 24 hours. (FF ¶ 40.) I conclude that that limitation is met for the same reasons I discussed with respect to the '887 patent. (CL ¶¶ 8-12.)

22. Again, the presence of the remaining limitations are not in serious dispute. Claim 1 also requires a "solid controlled release oral dosage form" containing a "therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof." ('430 patent, 12:41-43.) Par's product is a tablet containing a therapeutically

effective amount of tramadol Hcl that provides a controlled release of the drug. (CL ¶¶ 13, 17.)

23. The '430 claims also require a "normal release matrix" with a controlled release coating. ('430 patent, 12:45-46.) Par's tablet core is a normal release matrix, as that term has been construed: dissolution tests on Par's uncoated tablet cores indicate that they release the active ingredient as quickly as feasible. (Davies Tr. 661:10-663:19; PTX-171 at PAR002024.)

24. Claim 3 of the '430 patent, from which asserted claim 5 depends, requires that the controlled release coating "comprises a water insoluble cellulose." ('430 patent, 12:54-56.) The coating on Par's tablet contains ethylcellulose, a water insoluble cellulose. (CL ¶ 20.) '430 claim 5 requires that the controlled release coating "further comprises a polyvinylpyrrolidone." ('430 patent, 12:61-63.) Par's tablet coating contains Povidone, a brand of polyvinylpyrrolidone. (Davies Tr. 662:4-7; PTX-166 at PAR015917.)

25. Claim 7 of the '430 patent requires the same *in vitro* dissolution profile as claim 3 of the '887 patent and is met for the same reasons. ('430 patent, 13:1-12; CL ¶ 14-16.)

26. Claim 11 of the '430 patent requires the same W_{50} value as claim 13 of the '887 patent and is also met for the same reasons. ('430 patent, 14:12; CL ¶ 19.)

B. *Validity*

27. A patent, along with each of its claims, is presumed valid, and "[t]he burden of establishing invalidity of a patent or any claim thereof shall rest on the party

asserting such invalidity." 35 U.S.C. § 282. Accordingly, the patent challenger bears the burden of proving the factual elements of invalidity by clear and convincing evidence. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). "That burden of proof never shifts to the patentee to prove validity." *Id.* Although a patentee has the burden of going forward with rebuttal evidence should a challenger present a prima facie case of invalidity, the trial court has the responsibility to determine whether the challenger has met its burden of proof by clear and convincing evidence by considering the totality of the evidence, "including any rebuttal evidence presented by the patentee." *Id.* at 1360.

28. Par challenges the validity of the patents-in-suit on three grounds: a lack of written description, anticipation, and obviousness. The following discussion is limited to obviousness because I conclude that the evidence clearly and convincingly shows that the asserted claims are invalid on that basis.[53]

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[53]In its post-trial papers, Par argues that the Oshlack patent (*see* FF ¶¶ 86-91), among other references, anticipates some of the asserted claims. Par contends that the "suitable for dosing every 24 hours" limitation in the '887 patent is disclosed because Oshlack teaches a dosage form that "preferably provides a therapeutic effect for about 24 hours." (PTX-601 at 4:56-59; *see* D.I. 340 at 37.) During claim construction, however, Par advanced the position that the "suitable for dosing" language was an indication of safety, not efficacy. (D.I. 161 at 12.) I adopted that position and accordingly ruled that the use of the term "every" in the "suitable for dosing" limitation did not bear on whether the claimed duration of therapeutic effect was to be measured in a steady state dosing environment. *Claim Construction Opinion*, 584 F. Supp. 2d at 675. Par's present argument as to anticipation with respect to the '887 patent, which equates "suitable for dosing every 24 hours" with the duration of therapeutic effect, is inconsistent with its position at claim construction, and I will not consider it.

However, the asserted claims of the '430 patent do not have the "suitable for dosing every 24 hours" limitation. Thus, Oshlack might anticipate asserted claims 7 and 11 of that patent as Par contends it does. (*See* D.I. 340 at 39.) Nonetheless, because I conclude that all of the asserted claims are clearly invalid as obvious in light

29. A claim is obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The ultimate determination of obviousness is a question of law, based on underlying factual determinations. *Altanta Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1007 (Fed. Cir. 2009). Those factual determinations include (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, known as objective indicia of non-obviousness. *Id.* (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

30. The Supreme Court recently rejected the rigid application of the principle that there should be an explicit "teaching, suggestion, or motivation" in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art, in order to find obviousness. *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007). Nonetheless, the *KSR* Court did acknowledge the importance of identifying "'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chems. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (quoting *KSR*, 550 U.S. at 418).

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of Oshlack, I need not decide whether claims 7 and 11 of the '430 patent are also invalid as anticipated by that reference.

31. When the prior art provides the means of making the invention and predicts the results, and the patentee merely verifies the expectation through "routine testing," the claims are obvious. *Pfizer*, 480 F.3d at 1367. In other words, obviousness exists when "a finite, and in the context of the art, small or easily traversed, number of options ... would convince an ordinarily skilled artisan of obviousness." *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (citing *KSR*, 550 U.S. at 421).

32. "While the presentation at trial of a reference that was not before the examiner does not change the presumption of validity, the alleged infringer's burden may be more easily carried because of this additional reference." *SIBIA Neurosciences, Inc. v. Cadus Pharmaceutical Corp.*, 225 F.3d 1349, 1355-56 (Fed. Cir. 2000).[54]

33. A person of ordinary skill in the art at the time of the invention was one with experience as a formulator, a pharmacokineticist, and a clinician. (FF ¶ 10.)

34. Some of the prior art on which Par relies post-dates the foreign priority documents listed on the face of the '887 patent. If Plaintiffs want to use the filing dates of those foreign priority documents to eliminate such prior art, they have the burden of going forward with evidence and argument that the asserted claims are entitled to the

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[54]I do not take the quoted language from *SIBIA* to mean that the use of a new reference at trial somehow changes a patent challenger's burden to something less than clear and convincing. Instead, *SIBIA* instructs that a reference not before the examiner may be strong evidence of obviousness. As a practical matter, assuming a new reference is closer to the asserted claims than the references before the examiner, one is not left to wonder, as one might be with a reference that was disclosed, why the examiner allowed the claims in light of the reference.

benefit of the foreign filing dates. *Technology Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327, 1329 (Fed. Cir. 2008). Plaintiffs have not carried that burden. Indeed, Plaintiffs do not dispute Par's argument that it has proven that the German priority document fails to provide a written description of the claimed subject matter (FF ¶ 69), nor do they rely on the filing dates of any other foreign document listed on the face of the '887 patent (FF ¶¶ 69-70). Thus, Plaintiffs are not entitled to rely on the filing dates of those documents to eliminate any of the prior art on which Par bases its obviousness case. The effective filing date of the patents-in-suit is May 10, 1994, the filing date of the original application for the patents-in-suit. (FF ¶¶ 66-67.)

35. The Oshlack and Kaiko patents are prior art under § 102(e) because they were granted on patent applications that were filed before the effective filing date of the patents-in-suit, namely July 27, 1993, and November 23, 1993, respectively.[55] (FF ¶¶ 86, 92.)

36. The Leslie and Lintz articles are prior art publications under § 102(b) because they were published more than a year before the effective filing date of the patents-in-suit, namely 1980 and 1986, respectively. (FF ¶¶ 17, 24.)

37. Having considered the competing arguments regarding the prior art, I conclude that the asserted claims are obvious in light of Oshlack.

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[55]Plaintiffs do not argue that the controlled release tramadol formulation claimed in the patents-in-suit were invented prior to the Oshlack and Kaiko patent applications. *See* 35 U.S.C. § 102(e)(2) (defining prior art to include "a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent").

38. Oshlack describes various controlled release oral dosage formulations, disclosing morphine, hydromorphone, and acetaminophen in specific examples, but broadly claiming that any "systemically active therapeutic agent[s]" may be used. (FF ¶ 87.)

39. Plaintiffs argue that it would not have been obvious for a person of ordinary skill to choose tramadol for a 24-hour controlled release formulation out of the "scores" of other analgesics or combinations disclosed in Oshlack. (D.I. 331 at 32.) Plaintiffs clearly overstate the size of the list in Oshlack, which claims tramadol as one of only 14 different "opioid analgesics." (FF ¶ 87.) But, more fundamentally, Plaintiffs fail to recognize that a prior art reference's inclusion of a claimed active agent in an undifferentiated list does not necessarily remove the reference from consideration as invalidating. "[T]o the extent [a patentee] suggests that the prior art must point to only a single [active ingredient] for further development efforts, that restrictive view ... would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in *KSR*." *Altana Pharma*, 566 F.3d at 1008.

40. Even before *KSR*, the patents-in-suit would likely have been considered obvious in light of Oshlack. In *Pfizer,* a pre-*KSR* case, the Federal Circuit held that a patent claiming a particular salt of a drug used to treat hypertension, amlopidine besylate, was obvious in light of Pfizer's earlier patent claiming amlopidine along with its pharmaceutically acceptable acid addition salts. 480 F.3d at 1353, 55. The invalidating reference described pharmaceutically acceptable addition salts of amlopidine generally, and then provided 12 examples, none of which was besylate. *Id* at 1353. Pfizer argued

that amlopidine besylate was not rendered obvious because the specific salts disclosed in the prior art were different in structure, and another prior art article that disclosed 53 FDA-approved substances that were useful for making pharmaceutically acceptable salts, including besylate, disclosed that besylate had a frequency of use of only 0.25%. *Id.* at 1361-62. The court rejected Pfizer's arguments, noting that there was only a "small" number of substances listed in the article and that other publications disclosed that besylate had favorable chemical characteristics. *Id.* at 1355, 63. The court found a clear motivation to combine the teachings of Pfizer's prior patent with other prior art to produce amlopidine besylate. *Id.* at 1364. Here, we are faced with an even clearer case of obviousness than *Pfizer*, as Oshlack itself discloses the active ingredient at issue, in an even smaller list, without so much as a hint that its use is uncommon.

41. Plaintiffs argue that the characteristics of tramadol that were known at the time made it an unlikely choice as compared to the other analgesics on the list. (D.I. 331 at 31.) For example, a 1992 paper by Dr. Robert Raffa, et al., reported that the clinical analgesic activity of tramadol is of an "atypical nature." (DTX-506 at 284; Grond, Tr. 982:18-25.) Studies of that sort, Plaintiffs argue, suggested that obstacles existed to successful development and regulatory approval that would have led a person of skill away from selecting tramadol and toward another active ingredient such as hydromorphone or acetaminophen, as Oshlack did in the '578 patent examples. (D.I. 334 at ¶ 128.)

42. But Raffa is far from a reference that teaches away from selecting tramadol. Although it does note tramadol's different mechanisms of action, it

emphasizes that such differences actually make tramadol more beneficial as an analgesic:

> Unlike typical opioid analgesics, the therapeutic use of tramadol has not been associated with clinically significant side effects such as respiratory depression, constipation (even after long-term administration) or sedation. In addition, analgesic tolerance has not been a significant problem during repeated administration, and neither psychological dependence nor euphoric effects are observed in long-term clinical trials. In addition, minimal withdrawal signs are observed in naloxone-precipitation studies, and tramadol does not appear to be suitable as a substitute in opioid-dependent patients. These clinical findings have been reinforced by the recent study of Preston *et al.* (1991) indicating that morphine-like subjective effects were less than those predicted by its analgesic potency relative to morphine.

(DTX-506 at 275-76 (citations omitted).)

43. Similarly, the Lintz article reported that because tramadol has good water solubility, is rapidly absorbed, has a long half-life and has high bioavailability relative to other centrally acting analgesics, "the duration of analgesia of tramadol is likely to be longer with equianalgesic doses and equal pain intensity than that of pentazocine and codeine." (FF ¶ 24.) Raffa and Lintz would each encourage a person of ordinary skill in the art to select tramadol as an active ingredient in a controlled release formulation.

44. Purdue's own Dr. Kaiko recognized as early as November of 1989 that tramadol was possibly more beneficial than other active ingredients, when he stated that tramadol "does not appear to be associated with psychotomimetic side effects," that it "appears to have less abuse liability and less respiratory depressant potential than opioid agonists (e.g. morphine, methadone, hydromorphone, oxycodone, levorphanol)," that it "has characteristics that make it suitable for oral ... administration," and that "clinical evaluations have generally concluded [tramadol] to be comparable or

superior to comparative agents." (PTX-26 at PUR0195200.) Rather than suggesting development and regulatory approval would be difficult, Kaiko counseled against using tramadol for an oral controlled release product simply because such a product would "cannibalize" other such products marketed by Purdue. (*Id.* at PUR0195201-202.) Perhaps more telling, Smith, one of the inventors listed on the patents-in-suit, wrote a note, later found attached to a translation of the German priority document, that asked "[w]hy is this not obvious (the developments from Lintz)[?]" (DTX-106 (emphasis in original); Smith, Tr. 52:5-54:22.)

45. This case is different from *Takeda Chemical*, 492 F.3d at 1352, on which Plaintiffs rely. (D.I. 331 at 32.) In *Takeda Chemical*, the Federal Circuit affirmed a district court's holding that a patent for a compound used to treat Type 2 diabetes was not invalid as obvious. *Id.* The party challenging the patent argued that a compound that was disclosed in the prior art would have been an obvious compound to select for further development and that, once selected, the development of the patented compound would have been obvious. *Id.* at 1354-60. Unlike here, however, the prior art disclosed "hundreds of millions" of available compounds. *Id.* at 1357. While the allegedly obvious choice was specifically claimed in some prior art and noted to be "especially important," another reference described the compound as having adverse effects, namely that it caused "considerable increases in body weight and brown fat weight," that would make the compound ill-suited for treatment of Type 2 diabetes. *Id.* at 1358-59. Because of that reference, the compound would not have been obvious to try. *Id.* at 1359 (citing *KSR*, 550 U.S. at 421). In contrast, the references the parties

rely on here all would suggest to a person of ordinary skill that tramadol was a particularly appropriate active ingredient for a controlled release analgesic.

46. Plaintiffs argue that the PTO allowed the claims as non-obvious even though it considered the same categories of prior art that are before me now. (D.I. 331 at 30.) That argument is not persuasive. Plaintiffs fail to acknowledge that the Oshlack and Kaiko references, part of the category of prior art describing pharmaceutical formulations that list tramadol, were not before the PTO and are directly on point. Moreover, the PTO did not have the benefit of the Supreme Court's opinion in *KSR*. Although I have been careful to give a presumption of validity to the patents-in-suit, the evidence is clear that the selection of tramadol as an active ingredient for a controlled release formulation would have been obvious even under pre-*KSR* case law and especially after *KSR*. As noted in that case, "when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." 550 U.S. at 416 (citing *United States v. Adams*, 383 U.S. 39, 50-51 (1966)).

47. I conclude that Oshlack either expressly discloses the remaining limitations in the asserted claims or contains differences that would have been established as a part of the routine experimentation involved in incorporating tramadol as an active ingredient. (*See* CL ¶ 31.)

48. Oshlack describes controlled release coatings comprising either hydrophobic (water-insoluble) acrylic polymers or polymethacrylates such as Eudragit®,

just as is claimed in the '887 patent claims 27 and 29 and the '430 patent claim 1. (FF ¶ 88.)

49. The dissolution profile given in Claim 43 of the Oshlack patent differs slightly from the dissolution profiles in the patents-in-suit in two related respects. First, Oshlack only provides dissolution ranges up to 8 hours, while the asserted claims provide ranges to 24 and 36 hours. (FF ¶ 89.) Second, the lower limit at 8 hours in claim 43 of Oshlack is lower than the narrowest range claimed by the patents-in-suit. (*Id.*) These differences do not render the asserted claims non-obvious. The upper limit on the ranges provided past eight hours in the asserted claims are all 100% and are therefore of no moment: any formulation would have a dissolution at or below 100%. The lower limits, however, require more attention. As discussed in the claim construction opinion, the specification indicates that the formulation becomes safer for once-a-day dosing as the dissolution range narrows. *Claim Construction Opinion*, 584 F. Supp. 2d at 675. Thus, because the upper limit in the dissolution ranges of the asserted claims are all at 100%, the lower limit suggests a cutoff that is necessary for the formulation to be suitable for once-a-day dosing. It appears that if the lower limit is too low — i.e., if only a small amount of the drug is dissolved into the blood stream early in the dosing cycle — large amounts of later-dissolving drug from the first pill could combine with early-dissolving drug from the second pill, potentially putting an unsafe amount of the drug into the blood stream at once. *Id.* If that is true, the formulation disclosed in Oshlack might not be suitable for once-a-day dosing, as the asserted claims require, if the formulation does not dissolve fast enough past eight hours.

50. Even though Claim 43 of Oshlack does require that the disclosed formulations have effective blood levels for about 24 hours, it does not require that those formulations be suitable for once-a-day dosing. (FF ¶ 90; *supra* note 53.) But controlled release formulations suitable for once-a-day dosing in general were not novel at the time of the filing of the '452 patent, nor were the claimed dissolution ranges. The Oshlack patent itself discloses an example of a controlled release preparation of morphine with dissolution data that falls within the claimed ranges through 16 hours and expressly notes that it is suitable for once-a-day administration. (FF ¶¶ 89-90.) Developing a controlled release formulation of tramadol that would fall within the claimed ranges and would be suitable for once-a-day dosing would have been obvious to one of skill in the art.

51. The obviousness of the dissolution profile in the asserted claims is made even more clear in light of Oshlack in combination with either Kaiko or the Leslie article. Kaiko discloses examples of controlled release formulations of morphine with dissolution rates that fall within the claimed ranges through 36 hours. (FF ¶ 93.) Even if it were the case that tramadol required dissolution limits on the low end that were higher than those required for other active ingredients such as morphine, perhaps because it takes longer for tramadol to pass the blood-brain barrier (*see* FF ¶ 14), the Leslie article taught a straight-forward way to vary the rate of dissolution through the Continus system. Napp relied on that system time and again to create successful controlled release products with different active ingredients. (FF ¶¶ 19-20, 30.) Although the number of options established by the prior art for creating a formulation

with appropriate dissolution rates appears to have been large (*cf.* FF ¶ 26; *supra* note 20), the evidence here establishes that they were relatively "easily traversed." *Ortho-McNeil*, 520 F.3d at 1364. Plaintiffs have done nothing to rebut the testimony of Dr. Palmieri that such adjustments would have been a result of "routine ... often dull laboratory experiments." (FF ¶ 20.)

52. Oshlack's failure to disclose a W_{50} value of 10 to 33 hours is inconsequential for the same reason — a W_{50} value in that range is a characteristic of a once-daily tramadol controlled release formulation that provides a therapeutic effect for approximately 24 hours and would be uncovered through routine experimentation. Indeed, Plaintiffs do not rely on the lack of a W_{50} value in Oshlack as a reason to differentiate the reference. Nor do they rely on Oshlack's failure to disclose the use of a polyvinylpyrrolidone as a choice for an excipient, as is required by '430 claim 5. That, too, would have been a routine choice that likely would have resulted from optimizing the controlled release formulation. (*See* FF ¶ 18.) The use of a formulation with a W_{50} value of 10 to 33 hours and a coating comprising polyvinylpyrrolidone yielded no more than a "predictable result." *KSR*, 550 U.S. at 416.

53. Oshlack does not disclose any PK data or show a target blood plasma profile for tramadol. (PTX-601 at 44:8-9; Oshlack, Tr. 191:21-192:5.) However, the Oshlack patent does disclose, in Claim 43, that tramadol controlled release formulations provide "effective blood levels ... for about 24 hours." (FF ¶ 90.) Even if PK data or target blood plasma profiles were required to enable the 24 hour claim limitation in Oshlack, they are not required to render the patents-in-suit obvious, as

enablement of the prior art is not a requirement to prove invalidity under § 103. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1357 (Fed. Cir. 2003). Instead, such information would be obvious based on Oshlack in combination with what was generally known in the art about tramadol (*see* FF ¶ 24 (discussing Lintz)) and controlled release formulations (*see* FF ¶¶ 17, 19-20 (discussing the Leslie article) and 93 (discussing Kaiko)).

54. The self-confessed expectation of success that the inventors had before beginning to work on controlled release tramadol, based on Napp's previous use of the Continus technology (FF ¶¶ 17, 25, 30), makes clear that there existed a "resoundingly" reasonable expectation of success in deriving the claimed invention in light of the teachings of the prior art. *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

55. In an effort to stave off a conclusion that the claims at issue are invalid for obviousness, Plaintiffs point to secondary considerations of non-obviousness, including Par's blatant copying and Ultram ER's commercial success. (D.I. 334 at ¶¶ 132-133.). However, secondary considerations of non-obviousness do not rebut a clear showing of invalidity. *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008). Moreover, a showing of copying, which Plaintiffs have provided here (FF ¶¶ 101-105), is not compelling evidence of non-obviousness in the Hatch-Waxman context. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, No. IP 99-38-C H/K, 2001 WL 1397304, at *14 (S.D. Ind. Oct. 29, 2001) ("[T]he ANDA procedures established by the Hatch-Waxman Act require generic drug manufacturers to copy the approved drug. Variations undermine the FDA's ability to assume that if the patented drug is safe and effective,

the generic competitor will also be safe and effective."). And, as to commercial success, while the promise of it remains (FF ¶ 99), the evidence of Ultram ER's sales to date is underwhelming (FF ¶ 98).

56. In sum, this case presents clear and convincing evidence of a situation where "a technique has been used to improve one [thing], and a person of ordinary skill in the art would recognize that it would improve similar [things] in the same way." *KSR*, 550 U.S. at 417. The asserted claims are therefore invalid as obvious in light of Oshlack, both on its own and in combination with Lintz, Leslie, or Kaiko.

C. *Inequitable Conduct*

57. Although it may not be necessary for me to decide Par's inequitable conduct charges in light of my invalidity ruling, *see Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1383 (Fed. Cir. 2007) (affirming district court's determination that inequitable conduct counterclaim was moot due to its determination that the asserted claims were invalid), I proceed to rule for the sake of completeness and in the interest of making public my opinion that Par has not carried its burden of proving that the Plaintiffs' employees and patent counsel engaged in inequitable conduct before the PTO.

58. "Inequitable conduct includes affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive." *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995). To successfully prove inequitable conduct, the accused infringer must prove by clear and convincing evidence at least a threshold level of both materiality and

intent to deceive. *Larson Mfg. Co. of South Dakota, Inc. v. Aluminart Prods. Ltd.*, 559 F.3d 1317, 1326 (Fed. Cir. 2009).

59. Information is material if a reasonable examiner would have considered such information important in deciding whether to allow the application. *Monsanto Co. v. Bayer Bioscience N.V.*, 514 F.3d 1229, 1237 (Fed. Cir. 2008). PTO Rule 56(b) also sets out a definition of material information as follows:

> [information that] is not cumulative to information already of record or being made of record in the application, and [that]
> (1) establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
> (2) ... refutes, or is inconsistent with, a position the applicant takes in:
> (i) Opposing an argument of unpatentability relied on by the Office, or
> (ii) Asserting an argument of patentability.

37 C.F.R. § 1.56. A misstatement or omission that is material under that definition is considered material for the purposes of an inequitable conduct inquiry. *Monsanto*, 514 F.3d at 1237.

60. To establish an intent to deceive the patent office, there must be clear and convincing evidence of "culpable" conduct. *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 560 F.3d 1366, 1380 (Fed. Cir. 2009). But direct evidence of intent is not necessary, and intent can be inferred from the surrounding facts and circumstances. *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005).

61. If threshold levels of both materiality and intent are found, the court must then determine, as a matter of law, "whether the questioned conduct amounts to inequitable conduct by balancing the levels of materiality and intent, with a greater showing of one factor allowing a lesser showing of the other." *Larson Mfg.*, 559 F.3d at

1327 (quotation omitted); *see Allen Organ Co. v. Kimball Intern., Inc.*, 839 F.2d 1556, 1567 (Fed. Cir. 1988) ("findings [of materiality and intent] ... are then balanced ... to determine whether as a matter of law the scales tilt to a conclusion that inequitable conduct occurred.") (quotation omitted).[56]

62. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the PTO, which includes a duty to disclose all information known to that individual to be material to patentability. 37 C.F.R. § 1.56. That duty extends to both applicants and their attorneys. *Brasseler, U.S.A. I, L.P. v. Stryker Sales Corp.*, 267 F.3d 1370, 1375 (Fed. Cir. 2001).

63. Inequitable conduct in prosecuting a patent may preclude enforcement of related patents if the inequitable conduct has an "'immediate and necessary relation'" to the enforcement sought. *Consolidated Aluminum Corp. v. Foseco Intern. Ltd.*, 910 F.2d 804, 810-11 (Fed. Cir. 1990) (quoting *Keystone Driller Co. v. General Excavator Co.*, 290 U.S. 240, 245 (1933)).

i. *Materiality*

64. Par argues that four pieces of material information were not forthrightly disclosed to the PTO. First, Par alleges that Plaintiffs should have disclosed the World

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[56]The Federal Circuit has been concerned with litigants' "'habit of charging inequitable conduct in almost every major patent case,'" calling it "'an absolute plague.'" *Ferring B.V. v. Barr Labs., Inc.*, 437 F.3d 1181, 1196 (Fed. Cir. 2006) (Newman, J., dissenting) (quoting *Burlington Indus. v. Dayco Corp.*, 849 F.2d 1418, 1422 (Fed. Cir. 1988)); *see Larson Mfg.*, 559 F.3d at 1342 (Linn, J., concurring) ("[Our] precedent has significantly diverged from the Supreme Court's treatment of inequitable conduct and perpetuates what was once referred to as a 'plague' that our en banc court sought to cure in *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876 n.15 (Fed. Cir. 1988) ... .").

Congress of Pain Abstracts and Grünenthal's prior work on a controlled release tramadol product. (D.I. 340 at 25.) Second, Par argues that Plaintiffs should have disclosed the Batch 616/07 and 616/07B experiments. (*Id.* at 26-27.) Third, Par argues that Plaintiffs failed to disclose the scientifically invalid experimental conditions surrounding the Malkowska I and II Declarations. (*Id.* at 27-28.) Fourth, Par contends that Plaintiffs belatedly submitted the results of the Napp repeat experiments, and, when they finally did submit those results, they buried them so that the examiner would not appreciate their significance. (*Id.* at 31-36.)

65. The World Congress of Pain Abstracts are not clearly and convincingly material. Par argues that the applicants should have disclosed the World Congress of Pain Abstracts because they rendered false a statement that the applicants made to the PTO in October of 1996, as a part of the prosecution of the original application for the patents-in-suit, that "no one, to the best of Applicants' knowledge and belief, has seriously suggested preparing an orally administragble [sic] controlled release formulation containing tramadol." (D.I. 339 at ¶ 115; DTX-11B at PAR45884-85.) But that was not a position that the applicants took in opposing a statement of unpatentability or asserting an argument of patentability. 37 C.F.R. § 1.56(b)(2). Instead, it was a throw-away statement made in response to an indefiniteness rejection for a claim that was simultaneously being amended. Specifically, the rejection concerned the claim, "a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration." (DTX-11B at PAR045875.) As the applicants acknowledged, the rejection, and necessarily their

statement in response, had been rendered "moot" by the amendment to that claim, which added, among other things, structural and dissolution limitations similar to those found in what is now claim 1 of the '887 patent. (*Id.* at PAR045875, 85.)

66. Grünenthal's assertions in its 1996 negotiations with Mundipharma that it had been testing controlled-release formulations for years before May 1993 are also not material because there is no indication that they were publicly known or used in the United States and, thus, they would not have qualified as prior art. 35 U.S.C. § 102; *see Carella v. Starlight Archery and Pro Line Co.*, 804 F.2d 135, 139 (Fed. Cir. 1986), *amended by* 1 U.S.P.Q.2d 1209 (Fed. Cir. 1986) ("The statutory language, 'known or used by others in this country' (35 U.S.C. § 102(a)), means knowledge or use which is accessible to the public.").

67. The failure of the Batch 616/07 run due to sticking was not material. Par does not contend that the dissolution data from that batch is material, and conditions unrelated to the earlier dissolution data submitted to the PTO were likely to blame for the sticking. (FF ¶ 123-124.) Thus, the problems of Batch 616/07 were irrelevant.

68. The non-disclosure of the Batch 616/07B run is more problematic. Plaintiffs argue that they did not need to disclose the second coating run because the spray rate was 2 g/min, whereas the tablets underlying the Malkowska I Declaration in 1995 were coated at a rate of 3 g/min (FF ¶¶ 125-126), and the purpose of the 1997 experiments was to duplicate the process conditions of the 1995 experiments. (D.I. 336 at 16.) Regardless of the purpose of the 1997 experiments, however, a reasonable examiner would have considered the results important. Merck/Bondi does not specify a

spray rate. (DTX-16.) That the lowered spray rate brings the dissolution results closer to the claimed ranges is an indication that one might be able to obtain the claimed controlled release tramadol formulation by following Merck/Bondi and making routine adjustments.

69. Plaintiffs argue that dissolution results that are closer to but not within the claimed ranges are irrelevant because a reference cannot inherently anticipate unless the results will "always occur by following the disclosure of the reference." (D.I. 334 at ¶ 179 (citing *In re Oelrich*, 666 F.2d 578, 581-82 (C.C.P.A. 1981)); D.I. 336 at 15.) However, that argument is no more than misdirection. It focuses on anticipation and completely ignores the pertinence of the Merck/Bondi reference as an obviousness reference. That an apparently routine adjustment in the coating spray rate causes the dissolution results to be significantly closer to the claimed ranges is indeed relevant to obviousness. (*See* CL ¶ 51.) Tellingly, the undisclosed dissolution results belie the statements in the Malkowska II Declaration that the results achieved by following Merck/Bondi were "significantly faster than" the EP '366 claims and "demonstrate no real control of the release of tramadol." (FF ¶ 130.) In view of the data that the applicants had in their possession, those statements in the Malkowska II Declaration were materially misleading. *See Monsanto*, 514 F.3d at 1240 (holding that internal notes were material because they "directly contradict arguments ... made to the PTO in support of patentability.").

70. The conditions of the experiments underlying the Malkowska I Declaration, however, did not need to be disclosed to the PTO. The above-100%

dissolution data included in the declaration did not necessarily indicate that an underlying problem existed with the experiments: Purdue's experts convincingly testified that dissolution data greater than 100% simply means that the tablet was manufactured with more than the expected dosage of tramadol. (Fanfarillo, Tr. 647:24-648:8; Davies, Tr. 671:6-672:10.) As to the false reporting of the average tablet core weight and the failure to report poor flow characteristics, those facts are clearly not helpful to Plaintiffs but ultimately are not important because the tablet weights were found to be within an acceptable range of the target weight. A contemporaneous laboratory notebook entry for the experiments shows that the tested tablets were weighed before coating and fell within the specified weight range of 352 mg, plus or minus 5 percent. Moreover, Brown remarked in that entry that, although the "flow properties were poor[,] [f]requent tapping of the hopper ... ensure[d] constant tablet weight." (Prater Tr. 140:22-45:6; PTX-490 at NAPP0372447; Prater, Tr. 152:19-53:19.) As to the inclusion of the dissolution data from only one tablet, that disclosure is not materially misleading because even the average dissolution rate fell outside the claimed ranges, and all of the tablets were tested under the same conditions. (Prater Tr. 1462:14-63:15.)

71. The results of the Napp repeat experiments were material, but they were properly disclosed. (FF ¶¶ 136, 141.) Par argues that Plaintiffs effectively failed to disclose the results because they did not submit the information immediately and, when they did submit it, they buried it in the middle of a lengthy IDS. (*See* FF ¶ 141.) That argument finds little support in fact or law.

72. Par argues that Davidson should have submitted the results of the Napp repeat experiments in his March 1999 IDS instead of continuing to rely on the

Malkowska Declarations. (D.I. 340 at 33.) However, the evidence suggests that all of the expert reports discussing those experiments might not have been disclosed in the U.K. Litigation until after Davidson submitted his March 1, 1999 IDS. (FF ¶ 140.) Davidson submitted those expert reports in the next IDS he submitted to the Patent Office. (FF ¶ 141.) That submission was sufficiently timely. *See Young v. Lumenis, Inc.*, 492 F.3d 1336, 1349 (Fed. Cir. 2007) ("The essence of the duty of disclosure is to get relevant information before an examiner in time for him to act on it, and that did occur here.").

73. Davidson did not improperly "bury" the results of the Napp repeat experiments by putting the Florence Supplemental Report in the middle of the March 2000 IDS. Davidson included a summary of each of the reports submitted, referenced the Florence Supplemental Report at the beginning of the section containing updated U.K. Litigation information, and went to the Patent Office to discuss the disclosed reports as a whole. (FF ¶¶ 141, 143-144.) Par points to no case that would impose a duty on Plaintiffs to disclose the results of the Napp repeat experiments in any other way.[57]

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[57]There is an undeniable tension between, on the one hand, cases that say that "[a]n applicant can not [sic] be guilty of inequitable conduct if the reference was cited to the examiner," *Fiskars, Inc. v. Hunt Mfg. Co.*, 221 F.3d 1318, 1327 (Fed. Cir. 2000), and those that say, on the other, that "'burying' a particularly material reference in a prior art statement containing a multiplicity of other references can be probative of bad faith," *Molins*, 48 F.3d at 1184. Patent lawyers must find the sometimes narrow middle ground between over-disclosure and under-disclosure, with the specter of an inequitable conduct charge on either side. Davidson found that middle ground, because he did more than simply submit the Florence and Fell supplemental reports along with a multitude of other references; he provided summaries of the reports and other references. He might not have put a red flag on the reports that Par now alleges are the most damning, but that fails to demonstrate that the references were improperly

74. In sum, the applicants did withhold material information and made two material misrepresentations to the PTO. Specifically, the Malkowska II Declaration withheld the dissolution test results of Batch 616/07B and instead argued that the teachings of the Merck/Bondi reference resulted in a formulation that dissolved "significantly faster than" the EP '366 claims and demonstrated "no real control of the release of tramadol." In fact, the withheld dissolution tests revealed results that were not significantly faster than those claims and that demonstrated that more control was possible. The conditions of the experiments underlying the Malkowska I Declaration, however, were not material, nor were the World Congress of Pain Abstracts or the unpublished information Grünenthal disclosed to Mundipharma. The results of the Napp repeat experiments, while material, were properly disclosed.

ii. *Intent to Deceive*

75. I focus my inquiry here on evidence that bears on whether the omission and misrepresentations relative to the Malkowska II Declaration were motivated by an intent to deceive, since those misrepresentations and related omission are the only material pieces of information that can be a basis for a decision that there was inequitable conduct. That is not to say, however, that deceptive intent with respect to the omission or misrepresentation of other, non-material information is never relevant. To the contrary, it might indeed be relevant to establishing that the applicant was acting deliberately when withholding the material information. Here, although the facts

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"buried." Davidson's earlier argument before the PTO that he could not choose between the various challengers' positions (FF ¶ 142) is persuasive here and helps to satisfy me that he fulfilled his duty of disclosure.

presented are disturbing, I ultimately conclude that Par has not sufficiently established that the applicants had an intent to deceive the PTO.

76. In the context of experiments done pursuant to prior art, the PTO is particularly at the mercy of applicants because, unlike with prior art searches, the PTO does not have the resources to conduct its own experiments. "[I]n submitting evidence of comparative tests ... an applicant must be held to be representing that his showing includes a fair and accurate demonstration of the closest prior art of which he is aware." *Norton v. Curtiss*, 433 F.2d 779, 792 (C.C.P.A. 1970).

77. The actions of the applicants in the preparation of the two Malkowska Declarations are striking. Malkowska clearly knew, and Prater likely knew, about the dissolution results of Batch 616/07B. (FF ¶ 128.) Malkowska might also have recognized their full import. (*Id.*) Yet instead of including those results, the Malkowska II Declaration suggested that the teachings of the Merck/Bondi reference were not helpful in obtaining the claimed controlled release formulation. (FF ¶ 130.) *See Monsanto*, 514 F.3d at 1241 ("Intent is easily inferred when, as here, an applicant makes arguments to the PTO that it knows, or obviously should have known, are false in light of information not before the examiner, and the applicant knowingly withholds that additional information."). In preparing the Malkowska I Declaration, Malkowska and Milnes altered and omitted certain test conditions, namely, the average weight of the tablets and the poor flow characteristics of the blend. (FF ¶¶ 113-114.) Moreover, for one of the experiments, they included data for only one tablet, the one falling the furthest outside of the claimed ranges, rather than the average tablet dissolution rate.

(*Id.*) Had the failure to include the average tablet dissolution rate been the only irregularity, then perhaps I would more readily believe that it was the result of simple oversight and that the one tablet chosen for analysis yielded the results it did by coincidence. But I cannot so easily dismiss that failure when coupled with the other altered and omitted test conditions found here. These facts are troubling.

78. But the standard of proof is high. It goes beyond suspicion and beyond proof by a preponderance of the evidence. The burden is to show by clear and convincing evidence that the applicants intended to deceive the PTO, and Par has failed to carry that burden. There is a plausible view of the evidence that does not involve intentional deceit. It is not far-fetched to conclude that the applicants were overly aggressive in trying to put a positive spin on the results of the experiments but that they did not intend to deceive anyone at the PTO. Applicants have a natural incentive to put things in a positive light, and there is a range of behavior, from simple spin to out and out deception, which may result from that incentive. Here, the possibility that the applicants were advocating their position without any deceptive intent is bolstered, to a limited but still significant degree, by three considerations. First, Malkowska's testimony that she did not recall why the dissolution results of Batch 616/07B were not disclosed in her declaration was, at this late date and given her demeanor, believable. (FF ¶ 130.) *Cf. Larson Mfg.*, 559 F.3d at 1341 ("[A]n accused infringer cannot carry its threshold burden simply by pointing to the absence of a credible good faith explanation."). Second, it is less than clear that the applicants who had knowledge of those dissolution results, applicants who were formulators rather than patent lawyers, recognized the import of those results on patentability. (FF ¶ 128.) *Cf.*

Dayco Products, Inc. v. Total Containment, Inc., 329 F.3d 1358, 1367 (Fed. Cir. 2003) ("[I]nequitable conduct requires not intent to withhold, but rather intent to deceive."). Third, and most importantly, the applicants did disclose the most damaging experimental results once they were completed following the Napp repeat experiments.[58] The Florence and Fell supplemental reports revealed experimental results that fell not just closer to, but within the claimed ranges. (FF ¶ 136.) The Posch report revealed the same thing. (FF ¶ 138.) It is clear from those reports that certain changes to the experimental conditions in Example 1 of Merck/Bondi can result in dissolution ranges that fall within the claimed ranges. That information is what Par correctly argues should have been disclosed to the examiner, and it was. (CL ¶ 74.) Because it ultimately was properly disclosed (CL ¶¶ 71-73), I cannot conclude, under the heightened standard of clear and convincing proof, that the applicants' failure to disclose similar information with respect to the Malkowska II Declaration was motivated by an intent to deceive. In short, Par's proof is incriminating, but not incriminating enough.

iii. *Balancing Materiality and Intent*

79. If adequate showings are made as to both materiality and intent, a district court must look to the equities and balance the substance of those showings to

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[58]That all the relevant information was eventually put before the PTO does not make the omission and misrepresentations contained in the Malkowska II Declaration any less material. The omission of information that forms the basis of affidavits, as opposed to omissions of prior art references, cannot be excused as cumulative of information otherwise before the PTO. "Affidavits are inherently material, even if only cumulative." *Refac International, Ltd. v. Lotus Development Corp.*, 81 F.3d 1576, 1583 (Fed. Cir. 1996).

determine whether the severe penalty of unenforceability should be imposed. *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1367 (Fed. Cir. 2008). Here, however, Par has failed to prove through clear and convincing evidence that the applicants harbored an intent to deceive the PTO, which leaves me with nothing to balance. *See Ariad Pharms*, 560 F.3d at 1380 ("Only after a district court makes independent findings of both materiality and intent may it weigh the two against each other in its ultimate determination of inequitable conduct."). I therefore conclude that Par has not established that the patents-in-suit are unenforceable for inequitable conduct.

IV. SUMMARY OF CONCLUSIONS

For the reasons set forth herein, Defendant Par's ANDA filing infringes claims 3, 13, 27, and 29 of the '887 patent and the manufacture, use, and offer to sell controlled release tramadol tablets in 100 mg, 200 mg, and 300 mg dosage strengths would infringe claims 5, 7, and 11 of the '430 patent. However, the asserted claims are invalid as obvious in light of the Oshlack patent and also in light of Oshlack in combination with Kaiko, Leslie, or Lintz. Finally, the patents-in-suit are not unenforceable due to inequitable conduct. An appropriate order follows.